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Towards Polymer Supported Iridium Borylation Catalysts for Organic Synthesis

Omar Abdullah Salih

Ph.D. Thesis

Supervisor: Professor Patrick G. Steel

University of Durham

Department of Chemistry

2016

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Declaration

The work described in this thesis was carried out in the Department of Chemistry at Durham University between July 2012 and June 2016, under the supervision of Prof. Patrick G. Steel. All the work is my own work, unless otherwise stated, and has not been submitted previously for a degree at this or any other university.

Omar Abdullah Salih

Acknowledgements

Foremost I would like to thank Allah for helping and giving me the power to complete this thesis. To my family who has suffered a lot in order to complete this work, I want to say thank you to my parents, my wife and my kids for their help and support during the period of study, even though a simple thanks you cannot express how much I apprieciate your support.

Many thanks for my supervisor Professor Patrick G. Steel for his guidance and ideas during the work in the lab. Thanks so much to Patrick's group and everyone who supported me and gave me advice in the lab and in my life during studying in the UK, Maria, David, Andrew, Chris Brown, Rebecca, Jay, Fieka and Elizabeth I will not forget their help in all my life.

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Last but not least, thanks a lot to all my friends in Durham especially Amjed Al-Qaisi for their help and support during the period of study.

Conferences Attended

1- NOSRC PG Symposium, 23rd October 2014 - Huddersfield University.

2- RSC Organic Division North East Meeting & Symposium, 6th April 2016 - The School of Chemistry - Newcastle University.

Abstract

The first chapter contains a detailed explanation of the borylation of arenes using iridium catalysts with different ligands. Phosphine, N,N-aryl and carbene ligands have been studied previously for the borylation of substituted aromatic and heteroaromatic compounds. The importance of polymer supported catalysts is shown. Examples of polymer supported iridium catalysts for the borylation of arenes are given. Chapter 2 discusses the preparation of 2-arylquinoline and quinolone derivatives. These were prepared by reaction of 3-methoxy and 3,5-dimethoxy aniline with malonic acid to generate the 2,4-dichloro quinoline derivatives. These in turn were then coupled with a range of aryl boronic acids in Suzuki-Miyaura cross-coupling reactions. A study documents the borylation selectivity of 2-(4'-methoxyphenyl)-4-chloro-7-methoxyquinoline **230.** Various conditions in Stille cross-coupling reaction were used to prepare nonsymmetrical 4,4'-substituted-2,2'-bipyridine derivatives **250** and **285** in chapter 3. These were prepared through coupling of stannyl pyridine **266** with 2-chloro- and bromo-4-substituted pyridine derivatives in presence of metal salts. Ligands **250** and **285** were evaluated in the borylation of m-xylene and compared to the activity of the literature standard ligand 4,4'-di-tert-butyl-2,2'-bipyridine dtbpy **22.** Chapter 4 describes the preparation of 2,4,6-substituted pyridine derivatives. These compounds were prepared by one of two methods. The borylation of 2-chloro-4-substituted pyridine derivatives afforded the corresponding boronate esters, which were then coupled with a range of aryl halides. This was followed by an aromatic nucleophilic substitution reaction with a range of amines. Alternatively, aromatic nucleophilic substitution of 2-chloro-4-substituted pyridine derivatives with amines afforded the corresponding 2-aminopyridines. Subsequent borylation of these

subtrates followed by Suzuki-Miyaura cross-copuling was also an effective strategy. Chapter 5 reports the synthesis of symmetrical phenanthroline **347** using the Altman protocol. Attachment of a linker to enable coupling to a polymer support afforded modified ligand **367**. Phenanthrolines **347** and **367** were evaluated in the borylation of m-xylene compared to the commercially available 3,4,7,8-tetra-methyl-1,10-phenanthroline tmphen **66**. The commercially available MCM-41 was chosen as a suitable polymer for the polymer supported iridium catalyst. Different strategies were investigated to attach the phenanthroline ligand to the polymer. These strategies involved attaching an amine linker to the polymer before coupling it with lithium phenanthroline carboxylate **368.** Chapter 6 provides all the experimental details.

Abbreviations

Aq – aqueous

Ar – Aryl

ASAP – atmospheric pressure solid analysis probe

ATR – attenuated total reflectance

box – 4,4’,5,5’-tetra-hydro-2,2’-bioxazole

Bpin – pinacolborane

bpy – 2,2’-bipyridine

BuLi – butyllithium

Cat – catecholato

Cat. – catalyst

COD – 1,5-cyclooctadiene

COE – 1,5-cyclootene

Cp – cyclopentadienyl

Cp^* – pentamethylcyclopentadienyl

diim – 2,3,5,6,8,9-hexahydrodiimidazo[1,2-a:2’,1’-c]pyrazine

dippe – 1,2-bis-(diisopropylphosphino)-ethane

DMA – dimethylacetamide

Dmabpy – 4,4’-dimethylamino-2,2’-bipyridine

DMAE – dimethylaminoethanol

DMAP – 4-dimethylaminopyridine

DMF – *N,N*-dimethylformamide

Dmobpy – 4,4’-dimethoxy-2,2’-bipyridine

dmpe – 1,2-bis(dimethylphosphino)ethane

DMSO – dimethylsulfoxide

dppe – 1,2-bis(diphenylphosphino)ethane

dppf – 1,1'-bis(diphenylphosphino)ferrocene

dtbpe – 1,2-bis-(di-ter-butylphosphino)-ethane

dtbpy – 4,4'-di-tert-butyl-2,2'-bipyridine

EDCI – *N*-ethyl-*N*'-(3-di-methylaminopropyl)-carbodiimide hydrochloride

EI – electron impact

eq. – equivalents

ESI – electrospray ionization

Et_3N – tri-ethylamine

etc. – *et cetera*

EtOAc – ethylacetate

GC-MS – gas chromatography-mass spectrometry

h – hour

HBcat – catecholborane

HBpin – pinacolborane

HBTU – *N*,*N*,*N*',*N*'-tetra-methyluronium hexafluorophosphate

HMDS – hexamethyldisilazane

HMBC – heteronuclear multiple bonds correlation

HSQC – heteronuclear single quantum coherence

Hz – Hertz

Ind – indenyl

IR – infrared

LC-MS – liquid chromatography-mass spectrometry

M – Molar

m.p – melting point

m/z – mass to charge ratio

Me – methyl

Mes – mesitylene

mg – milligram

Min – minute

µl – microliter

ml – milliliter

mmol – millimole

MTBE – methyl-*tert*-butylether

µW – microwave

NMR – nuclear magnetic resonance

NOESY – nuclear overhauser effect spectroscopy

o – *ortho*

p – para

pin – pinacolato

PMe_3 – tri-methylphosphine

ppm – parts per million

r.t – room temperature

TFA – tri-fluoroacetic acid

THF – tetra-hydrofuran

TLC – thin layer chromatography

Tmphen – 3,4,7,8-tetra-methyl-[1,10]-phenanthroline

UV – ultraviolet

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Chapter 1

1 Introduction to this thesis

Due to the widespread use of iridium metal in organic synthesis, such as the formation of C-B bonds, which in turn are used as intermediates in many different reactions, it is necessary to recycle the iridium catalyst to keep this metal from running out in the future. One method of particular interest is immobilising the iridium catalyst onto a polymer and the work described in this thesis is directed towards this goal. This thesis is composed of six chapters: The first chapter reviews the background of the borylation of heterocycles, and different ligands in the borylation of arenes which could be used as useful intermediates to attach to a polymer in polymer supported iridium catalysts. Chapter 2 discusses the borylation of quinoline derivatives that have potential applications in biological chemistry studies. Chapter 3 covers the formation of new bipyridine ligands with suitable linker, which could be applied in polymer supported iridium catalyst. Chapter 4 involves the development of one-pot C-H borylation/ Suzuki-Miyaura cross coupling reaction sequences followed by S_NAr reactions as a highly efficient strategy in the preparation of 2,4,6-substituted pyridines. Chapter 5 applies the same strategy to form a polymer supported ligand in chapter 3 to phenanthroline ligands. The last chapter of this thesis contains all the experimental procedures for the chapters 2, 3, 4 and 5.

1.1 CH Borylation

1.1.1 Introduction

Aromatic boronate esters have become one of the most important classes of reagents in organic synthesis.[1] With many applications in diverse transformations such as the Suzuki-Miyaura cross coupling,[2-6]rhodium catalyzed conjugate addition to α,β-unsaturated carbonyl compounds[7] and the Cu catalyzed synthesis of C-O and C-N bonds[8] (**Figure 1**).[9] One example of this from our group is Tajuddin's report.[10] Tajuddin synthesised many functionalized aromatic and heteroaromatic compounds which were prepared by borylation and subsequent Suzuki-Miyaura cross-coupling reactions, or by rhodium-catalysed 1,4-conjugated addition reactions.

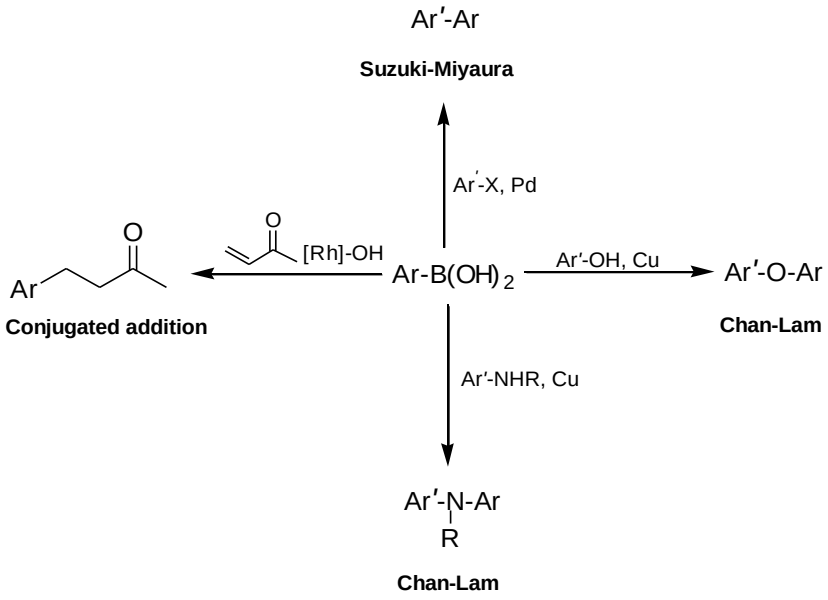
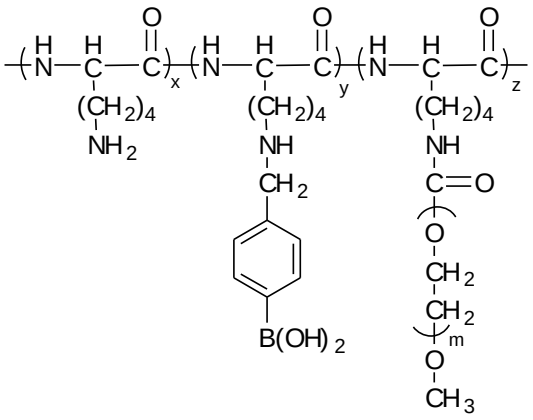


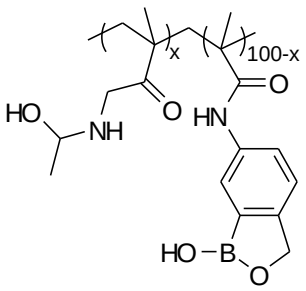
Figure 1: Some applications of aryl boronic acid

Reflecting this as shown in **Figure 1**, the synthesis and subsequent reaction of boronic acids has been key to the preparation of new drugs and herbicides. For example, boronic acid containing macromolecules have been utilized in some biomedical applications, including the treatment of HIV, multiple myeloma and diabetes as

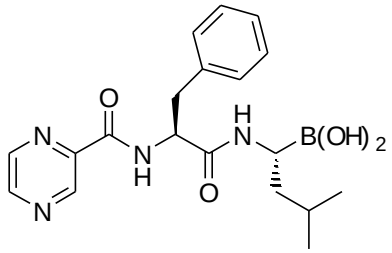
saccharide sensors (**Figure 2**).[11] Moreover, other biomedical applications of boronic acids include cell capture and culture and enzymatic inhibition agents (**Figure 2**).[12,13]



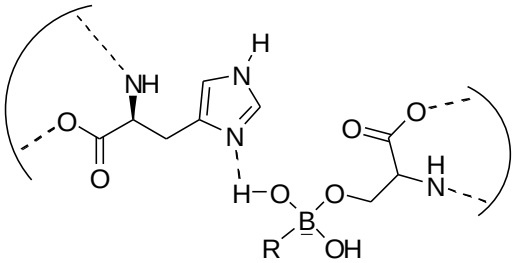
PLL-g-(Poly(ethylene glycol);phenyl boronic acid) as cell capture and culture



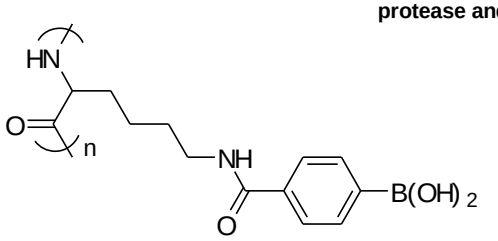
Poly(2-hydroxypropylmethacrylamide(PHPMA)-co-poly-(5-methacrylamido-2-hydroxymethyl phenyl boronic acid for the HIV inhibition



Bortezomib (Velcade) for the treatment of multiple myeloma



Boronic acid inhibition of seren protease and lipase enzyme

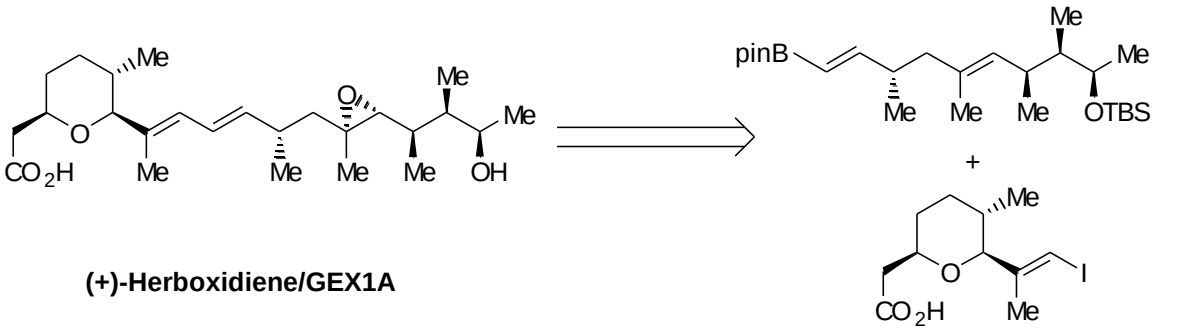


Saccharide sensor

Figure 2: Some biomedical applications of boronic acid[11-13]

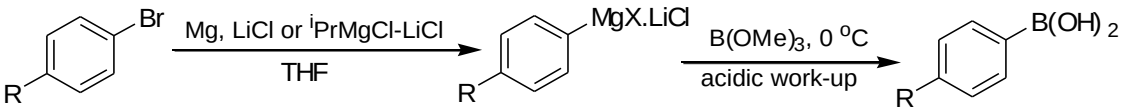
Boronic acids can not only be used in new functional materials, but are an essential component in many natural product syntheses as well (**Figure 3**).[14-17] Therefore, methods for the synthesis of aryl boronate ester are valuable. This review will briefly

summarise classical methods before focusing on the Ir-catalyzed borylation of aromatic C-H bonds with a particular emphasis on heteroarenes as substrates.


Me
O
Me
Me
Me

1.1.2 Synthesis of aryl boronate esters or boronic acids

Classical approaches to the synthesis of aryl boronate esters **5** and **6** involve the treatment of tri-alkyl borates with aryl Grignard or lithium reagents **3** and **4** (**Scheme 1**).[18]



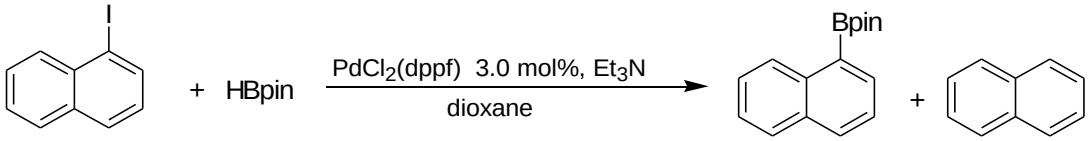
1 (R= OMe)
2 (R= CN)

3 (R= OMe)
4 (R= CN)
X= Cl, Br

5 (R= OMe) (92%)
6 (R= CN) (72%)

Scheme 1: Preparation of aryl boronic acids using Grignard reagent[18]

This method is the cheapest and most commonly used to prepare aryl boronic acids. However, this reaction needs cryogenic conditions (-78 ^{o}C (Li) and up to -10 ^{o}C (Mg)) that complicate large scale preparations. Moreover, this method is limited to substrates that are stable in the presence of nucleophilic and basic reagents. Another method to prepare aryl boronate ester **8** involves using palladium catalysts such as $PdCl_2$(dppf) and the pinacol ester of diboronic acid B_2pin_2 or pinacol borane HBpin with 1-iodonaphthalene **7** (**Scheme 2**).[19]



7

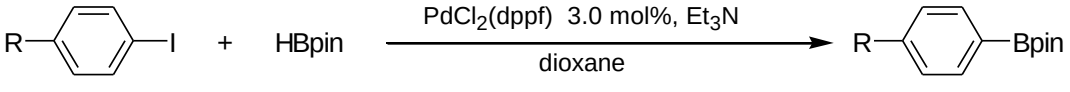
8 (89%)

9 (6%)

Scheme 2: Preparation of aryl boronate esters using Pd catalysis[19]

This method is considered a good method for synthesis of arylboronate esters **8, 12** and **13**. This reaction tolerates different functional groups on the aryl halides including

electron-donating and electron-withdrawing groups **10** and **11** (**Table 1**).[19] However, this reaction is only viable for the more reactive aryl halides such as aryl iodides and bromides rather than aryl chlorides.

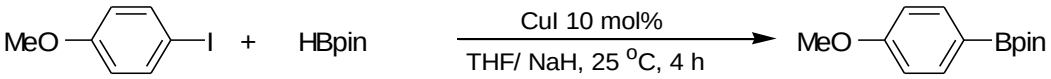


10 (R= Me)
11 (R= NO_2)

Comp No	R	Yield%
12	CH_3	79
13	NO_2	84

Table 1: Preparation of aryl boronate esters[19]

More recently, aryl boronate esters such as **15** have been prepared by the reaction of haloarene **14** with pinacolborane **(Scheme 3**)[20] catalyzed by copper iodide in presence of a strong base such as sodium hydride.



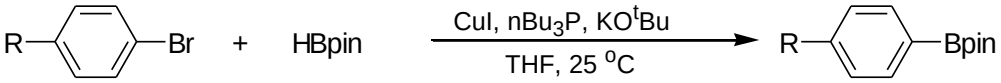
14

15 (75%)

Scheme 3: Preparation of aryl boronate ester by copper catalysis[20]

Copper catalysts are the cheapest for the preparation of aryl boronate esters and this reaction gives high yields of aryl boronate esters when using sodium hydride as a base. However, this method gives poor yields of aryl boronate esters when using aryl bromides. This could be due to the slower rate of oxidative addition of the aryl bromide compared to the aryl iodide. More recently, Marder and co-workers prepared arylboronate esters **12** and **18** using CuI with nBu_3P. This reaction is viable for aryl

iodides and bromides that contain either electron-rich or electron-deficient groups **16** and **17** (**Table 2**).[21]

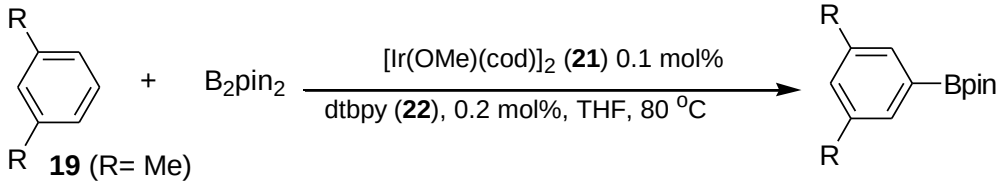


16 (R= Me)
17 (R= CF_3)

Comp No	R	Yield%
12	CH_3	83
18	CF_3	65

Table 2: Preparation of a phenyl boronate ester from an aryl bromide[21]

Although there are many methods to prepare boronic acids or boronate esters,[22] there are drawbacks for each. This section illustrates this problem by reviewing the major methods. The disadvantage of these C-X borylation strategies is the need to have a halogenated starting material. Ir/catalyzed C-H borylation is another method used to form aryl boronate esters **23** and **24,**[23] and one in which aryl halides are avoided. This involves borylation of a C-H bond using $[Ir(OMe)(cod)]_2$ **21** with dtbpy **22** in presence of boron source**.** A second advantage of this approach is tolerance to a variety of electron-donating and electron-withdrawing groups **19** and **20** (**Table 3**).[23]



19 (R= Me)
20 (R= CF_3)

Comp No	R
23	CH_3
24	CF_3

Table 3: Borylation of arenes using Ir-Catalysis[23]

Thus, iridium C-H borylation has been reported and discussed for a variety substrates. The next section will focus on Ir- catalyzed C-H borylation and starts with the history of the borylation, mechanism and previous work in the group.

1.1.3 History

The first example of Ir catalyzed C-H borylation occurred in 1993 when Marder *et al*. [24] reported that a small amount of C-H borylation was observed during the preparation of iridium tris-boryl complex [(η^6-C_6H_5Me)Ir(Bcat)$_3$] **27** (**Figure 4**). This was prepared in the reaction of [(η^5-indenyl)Ir(cod)] **25** with excess HBcat in toluene **26**, resulting in a small amount of tolylBcat **28** and **29** as identified by GC/ MS.[24] In 1995[25] Hartwig *et al.* reported that the borylation of toluene **26** in stoichiometric photolytic reactions occurred using catalysts such as [Mn(CO)$_5$(Bcat)], [Fe(Cp)(CO)$_2$(Bcat)] and [Re(CO)$_5$(Bcat)] (**EQ 1**) (**Scheme 4**). Additionally the same group[26] used Cp*Mn(CO)$_3$ **30** with benzene **31** in presence of B_2pin_2 to prepare phenyl boronate ester **32** (**EQ 2**) (**Scheme 4**).

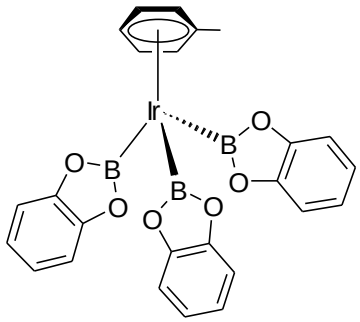
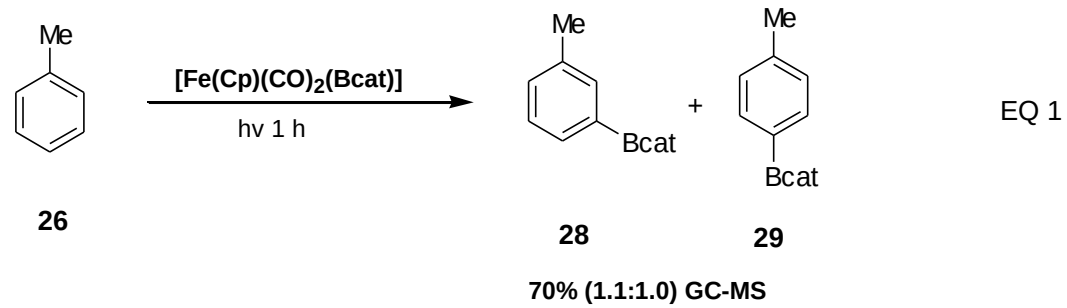
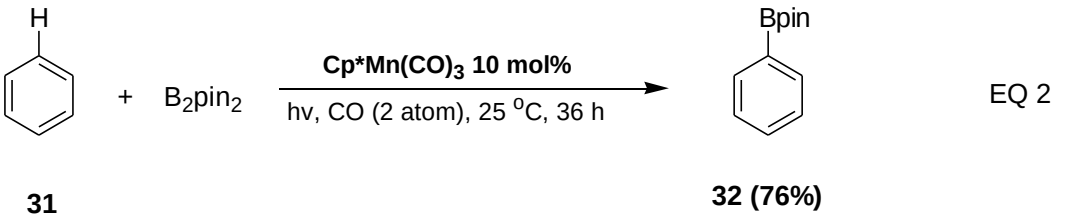


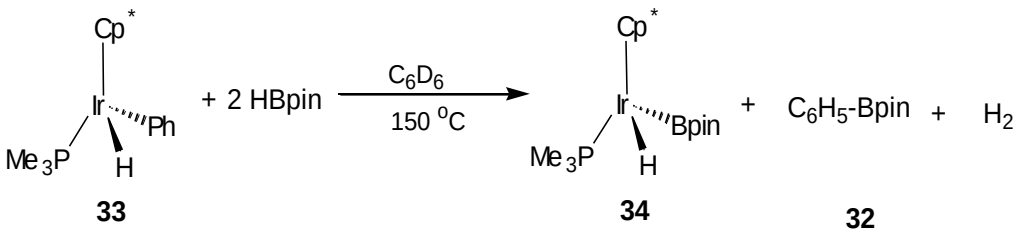
Figure 4: Structure of tris-boryl complex 27[24]



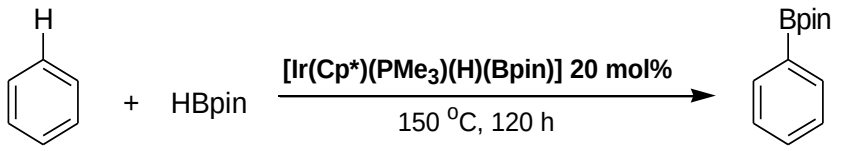


Scheme 4: Photolytic aromatic borylation[25,26]

Subsequently, in 1999[27] Iverson and Smith demonstrated a stoichiometric thermal reaction using HBpin with [Ir(Cp*)(PMe$_3$)(H)(Ph)] **33** to form the complex species [Ir(Cp*)(PMe$_3$)(H)(Bpin)] **34** together with the phenyl boronate ester **32** (**Scheme 5**). It was found that an aromatic C-H borylation could be obtained through using complex **34** with HBpin at 150 °C for example borylation of benzene **31** needed 120 h to afford a 53% yield of arylboronate **32** (**Scheme 6**).[28]



Scheme 5: Thermal method to form phenyl boronate 32[27]

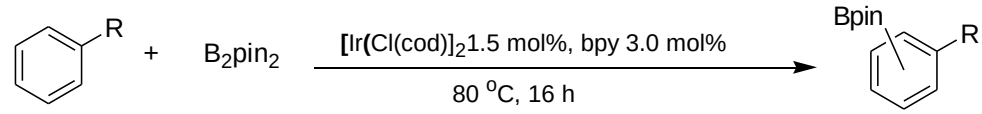


31 **32 (53%)**

Scheme 6: Borylation of arenes using [Ir(Cp*)(PMe$_3$)(H)(Bpin)] 34[28]

In 2002 Hartwig *et al*.[29] and Smith[30] independently reported that the C-H activation of arenes takes place using [Ir(Cl)(cod)]$_2$. Hartwig *et al*. found that arylboronate esters **32** and **39-41** could be obtained by the borylation of arenes (**26**, **31**, and **35-36**) with B_2pin_2 catalyzed by [Ir Cl(cod)]$_2$ **37** and 2,2'-bipyridine **38** at 80 °C (**Table 4**).[28] This gave nearly a 2:1 ratio of *meta*- to *para*-borylated products for mono-substituted arenes with both electron-rich and electron-poor groups. The only exception to this selectivity is the borylation of anisole, which may be explained by the coordination of the oxygen of the methoxy group to the iridium catalyst leading to activation of C-3.[31] Moreover, this reaction can take place at room temperature when using dtbpy **22**.[28] In the same year Ishiyama *et al*. also reported[32] that the phenyl boronate esters can be prepared by reaction of arenes with a complex of tris(boryl) species Ir(Bpin)$_3$(dtbpy)(COE) **42**. The nature of the precatalyst complex impacts on the efficiency and rate of the borylation reaction. For example, it was found[33] that a turnover number of 8000 was achieved through using 0.02 mol% 1/2[IrCl(coe)$_2$]$_2$ **43** with dtbpy **22** at 100 °C. However, this reaction proceeds smoothly at room temperature using [Ir(OMe)(cod)]$_2$ **21** with dtbpy **22**.[34,35] In general active catalysts **88A (Section 1.1.5, Figure 8,**) generated from [IrX(cod)]$_2$ pre-catalysts (where X= OH, OPh and especially OMe) offer faster reaction times than the chloro derivative.[33,34] Since then there has been a large value of literature

explaining the variables that affect the efficiency of this reaction. There is too much to cover in the space available and, reflecting the focus of this thesis, the next section will concentrate on the role of the ligand in this process.



31 (R= H), **35** (R= OMe)
26 (R= Me), **36** (R=CF_3)

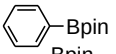
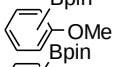
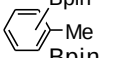
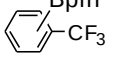
Prod No	R	Ar-Bpin	Yield% (o:m:p)
32	H		95
39	OMe		95 (1:74:25)
40	Me		82 (0:69:31)
41	CF_3		80 (0:70:30)

Table 4: Preparation of phenyl boronate esters[28]

1.1.4 Ligands Discussion

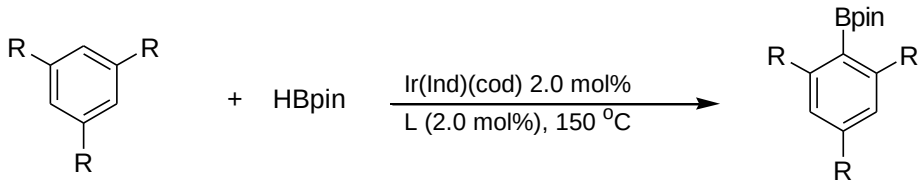
1.1.4.1 Introduction

In addition to the nature of the metal complex used, the nature of the ligands plays a major role in the iridium catalyzed C-H borylation reaction. Reflecting this, many different ligands have been described including phosphines, hydrazones, carbenes etc. This section will review the different ligands based on the nature of the ligating atoms/ group.

1.1.4.2 Phosphine based Ligands

The first examples of arene C-H borylation were reported, using a iridium tris boryl complex with Cp^* or indenyl ligand systems.[24,27] These reactions were either

stoichiometric reactions or showed low TON. The key breakthrough was reported by Smith and co-workers who introduced phosphine ligands which provide the first example of substoichiometic reactions (**Section 1.1.3**, **Scheme 6**).[28] Subsequently Smith and coreported the use of bidentate phopshines such as PMe_3 **44**, dppe **45** and dmpe **46** with an Ir(Ind)(cod) pre-catalyst **25** and HBpin as the boron source in the borylation of arenes **31** and **47** to afford arylboronate esters **32** and **48**[30]. It was found that the highest yields of borylated product were obtained, using a 2:1 ratio of PMe to Ir-precursor or 1:1 ratio of dmpe and dippe to Ir-precursor to generate the catalytically active species which is believed to be the trisboryl complexes $Ir(Bpin)(PR_3)_n$. This species tolerated a variety of functional groups, both electron-donating and electron-withdrawing (**Table 5**).[36]



31 (R= H)
47 (R= F)

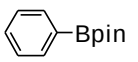
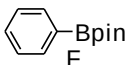
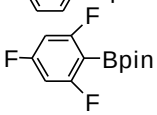
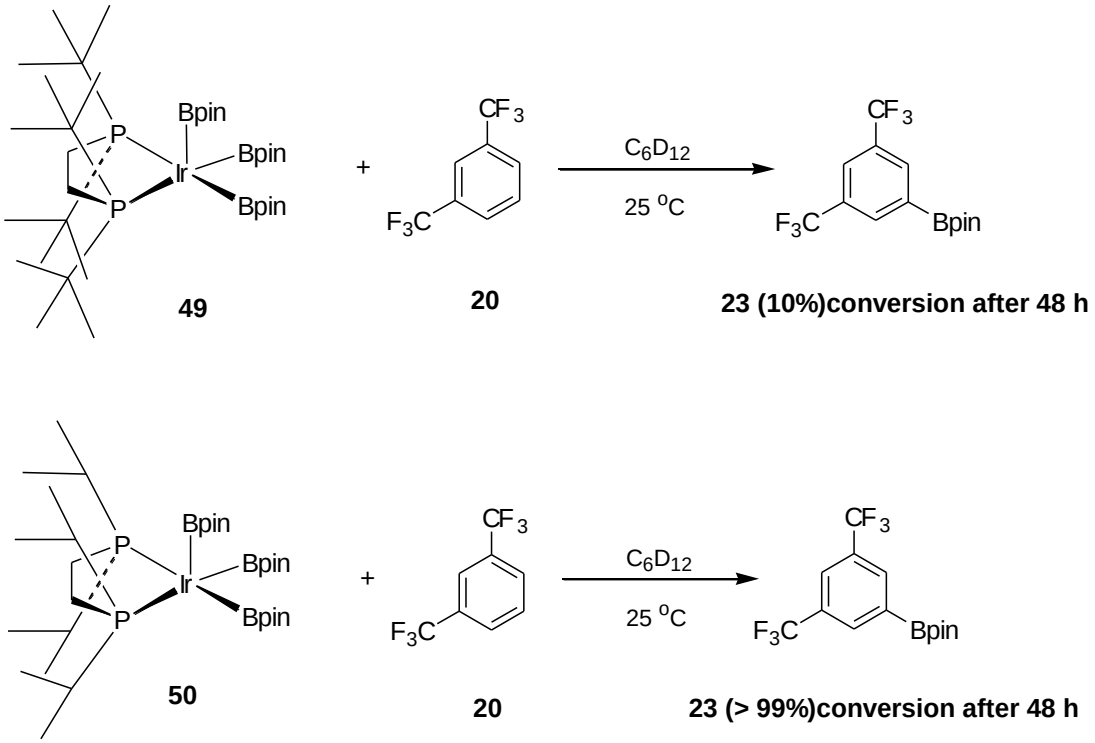
Compd No	R	(L)	Ar-Bpin	Yield%
32	H	**44**		88
32	H	**45**		95
48	F	**46**		63

Table 5:Borylation of arenes using $Ir(Bpin)(PR_3)_n$[36]

Steric factors also play a significant role. For example borylation using Ir(Bpin)(dippe) **50** afforded a > 99% conversion of 1,3-di-(tri-fluoromethyl)benzene **20** after 48 h at 25

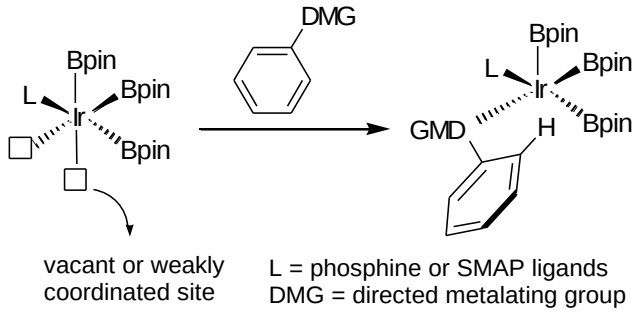
^{o}C whereas the use of the corresponding t-butyl ligand dtbpe (complex **49**) afforded only a 10% conversion (**Scheme 7**).[37]



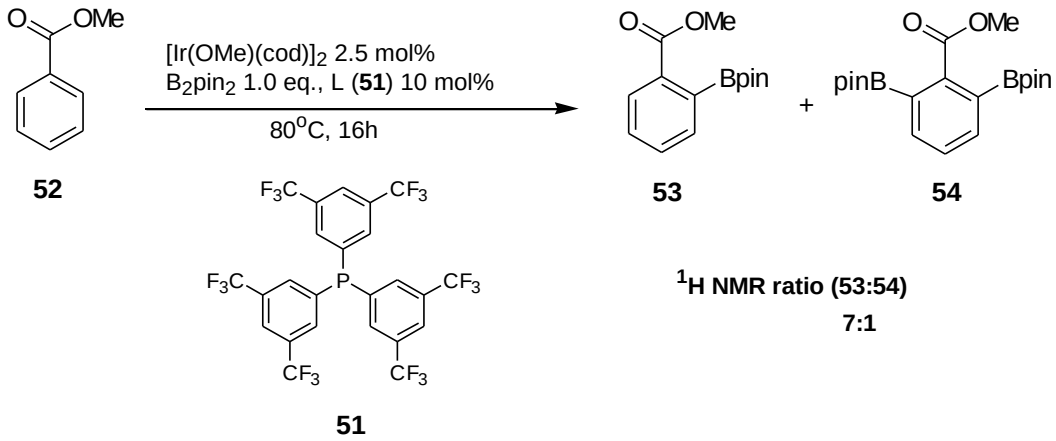
Scheme 7: Borylation of 1,3-CF_3-C_6H_4 using dippe and dtbpe ligands[37]

More recently, monodentate phosphine ligands have been developed as these can enable directed boryaltion of specific substrates. Electron-poor phosphine ligands can dissociate and allow the carbonyl oxygen of the substrate to coordinate to the iridium complex (**Scheme 8**).[38,39] Ishiyama, Miyaura and co-workers were able to use monodenate phosphine ligands with $[Ir(OMe)(cod)]_2$ **21** for the borylation of arenes.[1,38] Preshlock reported that the borylation of methylbenzoate **52** using 3,5-$(CF_3)_2(C_6H_3)_3P$ **51** afforded a 7:1 mixture of mono- and bis-borylated products **53** and **54** (**Scheme 9**).[40] A silica-supported monophosphine ligand **55 (Figure 5),** reported by Sawamura, also enabled directed *ortho*-borylation of methylbenzoate derivatives **56-58** to afford

the aryboronate ester **59-61** (**Table 6**).[41] Although an electron-rich phosphine ligand is used in this process, the silica supported phosphine ligand forms a mono phosphine complex, which allows coordination of the carbonyl oxygen to the iridium centre. Methoxy-substituents in 2- or 4-positions of methylbenzoate have minor effects on the borylation reaction. This could be due to the stronger coordination of the carbonyl oxygen of the substrate to the iridium centre compared to the methoxy group. Ligand **55** was also used for the directed *ortho*-borylation of phenol derivatives such as **62** (**Scheme 10**).[42]



Scheme 8: *Ortho* borylation strategies with DMG[39]



Scheme 9: Directed *ortho*-borylation of methylbenzoate 52 using 51 ligand[40]

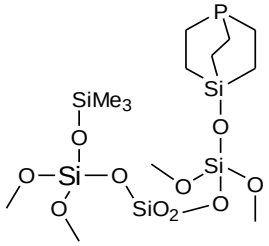
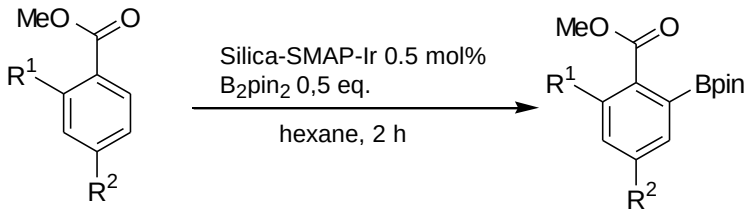


Figure 5: Silica-SMAP ligand 55[41]

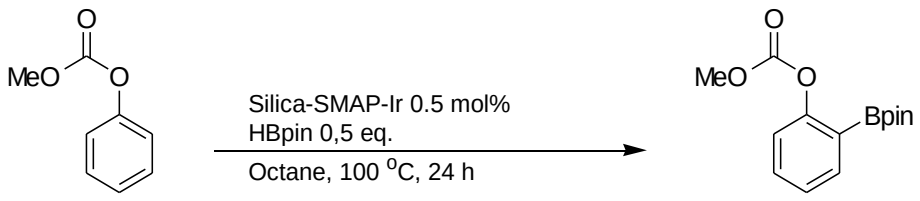


56 = R^1, R^2= H
57 = R^1= OMe, R^2= H
58 = R^1= H, R^2= OMe

Comp No	R^1,R^2	T ^oC	Yield%[a]
59	H,H	25	89
60	OMe, H	25	85
61	H, OMe	40	96

[a]isolated yield of product based on B_2pin_2

Table 6: Borylation of methylbenzoate derivatives using a Silica-SMAP-Ir 55[41]



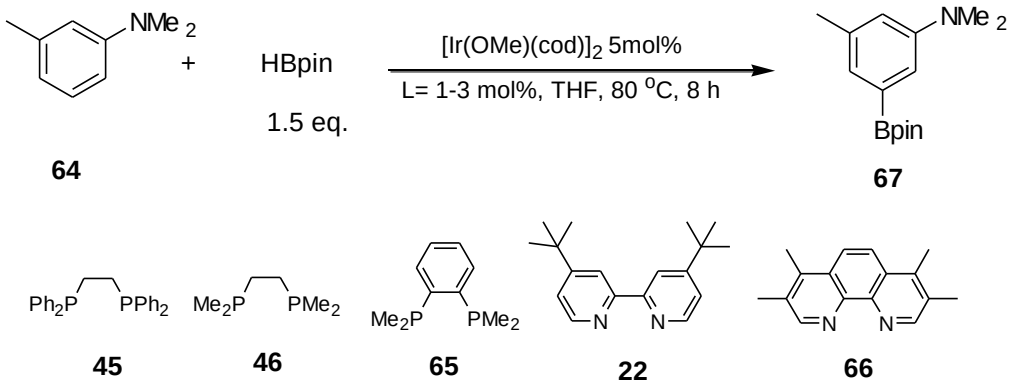
62 **63**

ratio o:(m+p) 100:0

Scheme 10: Borylation of phenol derivatives using a Silica-SMAP-Ir 55[42]

1.1.4.3 N-N based Ligands

Although phosphine ligands make functional catalysts in the borylation reaction, Iridium catalysts generated with nitrogen chelating ligands have been found to provide higher reactivity.[30] For example, it was found that the borylation of 3-methyl-*N*,*N*-dimethylaniline **64** using $[Ir(OMe)(cod)]_2$ **21** and dppe **45**, dmpe **46** and dmpbz **65** did not give the borylated product whereas using the ligands dtbpy **22** and tmphen **66** afforded mono-borylated product **67** (**Table 7**).[43] The active catalyst bearing phosphine ligands likely requires higher temperatures in order to display improved reactivity.



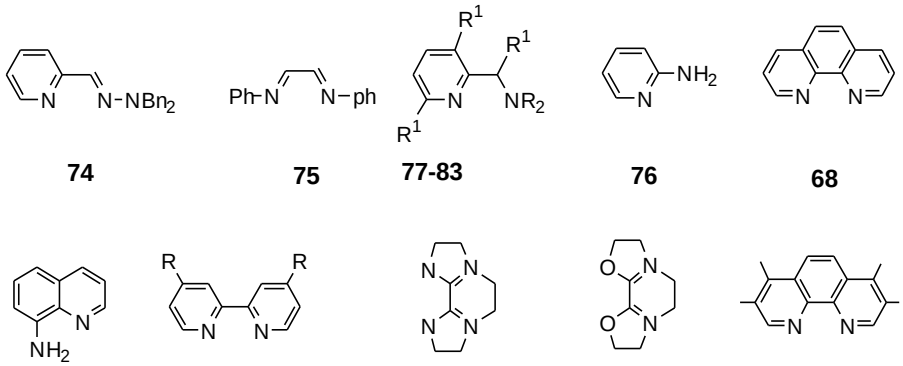
entry No	(L)	yield%[a]
1	**45**	0
2	**46**	0
3	**65**	0
4	**22**	14
5	**66**	64

[a]yields determined by HPLC

Table 7: Borylation of 3-methyl-*N*,*N*-dimethylaniline using different ligands[43]

Recently a variety of N,N bidentate ligands have been used in the borylation of arenes including tmphen **66**, phene **68**, dtbpy **22**, dmobpy **69**, dmabpy **70**, 8-aminoquinoline **71**, box **72**, diim **73**, hydrazone **74**, imine **75** and pyridine amine derivatives (**76** and **77-83**) (**Figure 6**).[40,44-46]Among N,N ligands, bipyridine ligands have shown high activity

in the borylation of arenes, as reported by Ishiyama, Miyaura, Hartwig and co-workers.[29,47] It was found that electron-donating functional groups at 4- and 4'-position of 2,2'-bipyridine such as OMe **69**, ^{t}Bu **22** and NMe_2 **70** improve the reactivity for the borylation of **31** and **86** with HBpin or B_2pin_2 resulting in arylboronate esters **32** and **87** (**Table 8, Table 9**) compared to electron-withdrawing groups such as Cl **84** and NO_2 **85**.[33]

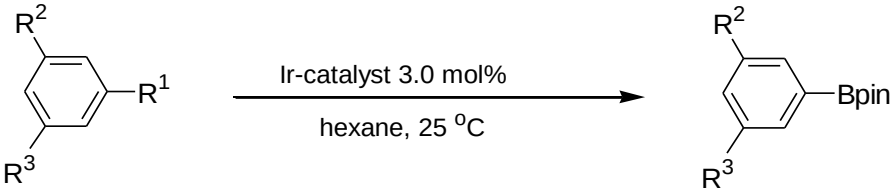


74 **75** **77-83** **76** **68**

71 **22 (R= ^{t}Bu), 69 (R= OMe)** **73** **72** **66**

70 (R= NMe_2)

Figure 6: Variety of *N-N* bidentate ligands using in the borylation of arenes[40,44-46]

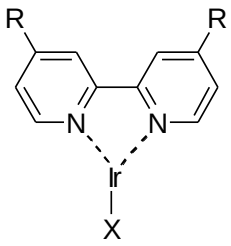


31 R^1, R^2, R^3= H

86 R^1= H, R^2, R^3= Cl

Comp No	R^1, R^2, R^3	Substrate (eq.)	Boron source	R. time (h)
32	H, H, H	excess	B_2pin_2	4
87	H, Cl, Cl	1.0	HBpin	8

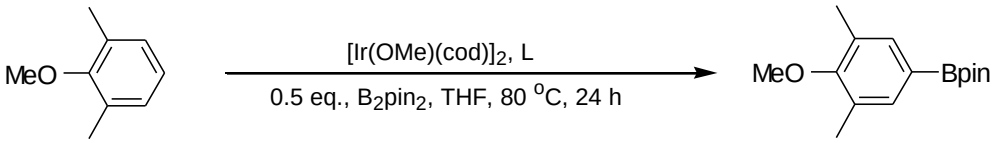
Table 8: Preparation of aryl boronate esters with Ir-Cat.[33]



entry No	Ir(x)	R	B_2pin_2%	HBpin%
1	$Ir(OMe)(cod)]_2$	NMe_2	88	88
2	$Ir(OMe)(cod)]_2$	OMe	90	27
3	$Ir(OMe)(cod)]_2$	^{t} Bu	83	86
4	$Ir(OMe)(cod)]_2$	Cl	0	7
5	$Ir(OMe)(cod)]_2$	NO_2	0	0

Table 9: The activity of dpy with different substitutions in 4- and 4'-positions[33]

Although 4,4'-disubstituted-2,2'-bipyridine such as dtbpy **22** show a good activity with the Ir-catalyst to generate the active tris-boryl species $Ir(Bpin)_3$(dtbpy) **88A**, low loading of $[Ir(OMe)(cod)]_2$ **21** ligated by tmphen **66** led to the most active catalyst in the borylation of **89** to afford Ar-Bpin **90** (**Table 10**).[43] It is unclear why tmphen under these conditions allows for the generation of a more active catalyst than dtbpy **22**. However it may be postulated that the increased planarity of tmphen could explain this difference in catalytic activity.

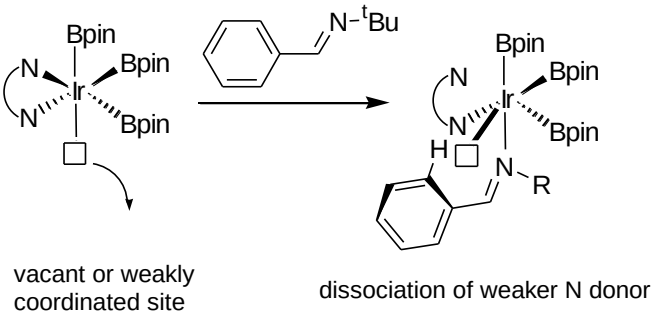


89 **90**

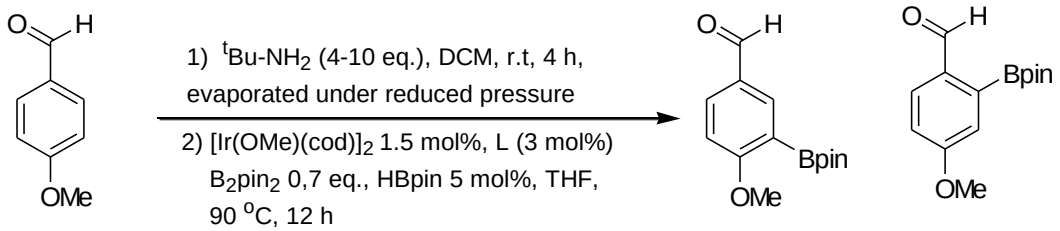
entry No	Ir mol%	(L) mol%		yield%
1	0.25	tmphen	1.0	84
2	1.5	dtbpy	3.0	56

Table 10: Borylation of 2,6-di-methylanisole using tmphen 66 and dtbpy 22[43]

Recently Chattopadhyay *et al.* used 8-aminoquinoline **71** with an Ir-catalyst in the borylation of substituted benzaldehydes using tert-butylamine as a protecting and directing group (**Scheme 11**) (**Table 11**).[44,45] This ligand **71** was compared with tmphen ligand **66** through the borylation of 4-methoxybenzaldehyde **91** to afford Ar-Bpin **92** and **93**. Ligand **71** showed selectivity of the borylation at *ortho* position of the imine group.



Scheme 11: Directed *ortho*-borylation of benzaldehyde in presence of ^{t}Bu-NH$_2$[45]

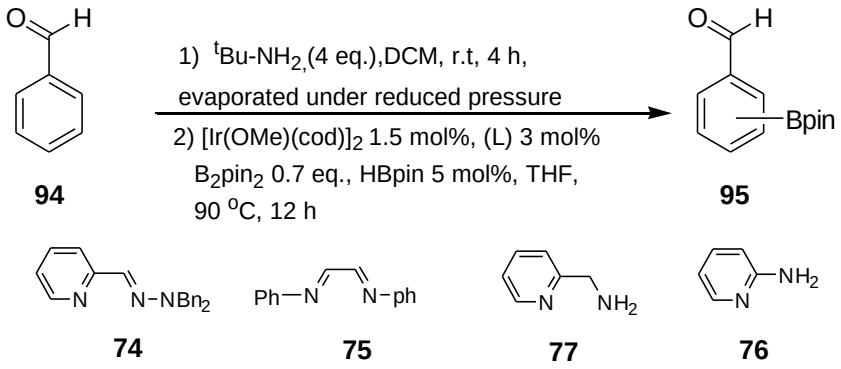


entry No	(L)	ratio (92:93)	yield%
1	**71**	0:100	60
2	**66**	81:19	74

Table 11: Borylation of 4-methoxybenzaldehyde using ligands 66 and 71[44]

Chattopadhyay also reported hemilabile bidentate ligands such as hydrazone derivatives (**74** & **75**) and pyridine amine derivatives (**76** & **77**) for the borylation of

unsubstituted benzaldehyde **94**. The reaction afforded a mixture of *meta*, *para* and *ortho* borylated products **95** (**Table 12**).[44] These reactions showed high selectivity for the *ortho*-borylated products, due to the coordination of the nitrogen of the imine group to the iridium centre.



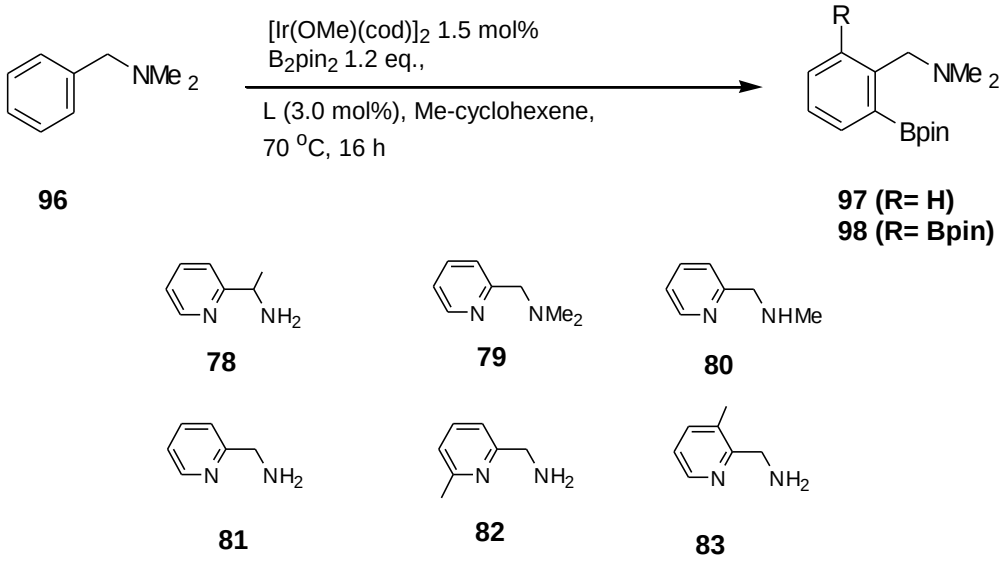
entry No	L	ratio[a] (o:m:p)	yield%
1	**74**	86:8:6	57[b]
2	**75**	100:0:0	66[c]
4	**76**	97:2:1	62[d]
3	**77**	95:2:3	72[e]

[a]ratios determined by GC-MS analysis [b]mono:o,o-di 90:10 [c]mono:o,o-di 80:20

[d]mono:o,o-di 85:15 [e]mono:o,o-di 87:13

Table 12: Borylation of benzaldehyde using pyridine derivatives[44]

Clark *et al.* also reported hemilabile amine ligands **78-83** (**Table 13**)[46] enabling directed *ortho*-borylation of *N*,*N*-di-methylbenzylamine **96** to afford a mixture of mono- and bis-borylated products **97** and **98**. *N*,*N*-Di-methylbenzylamine **96** coordinates to the iridium centre alongside the diamine.[48] This facilitates the directed borylation of substrate.



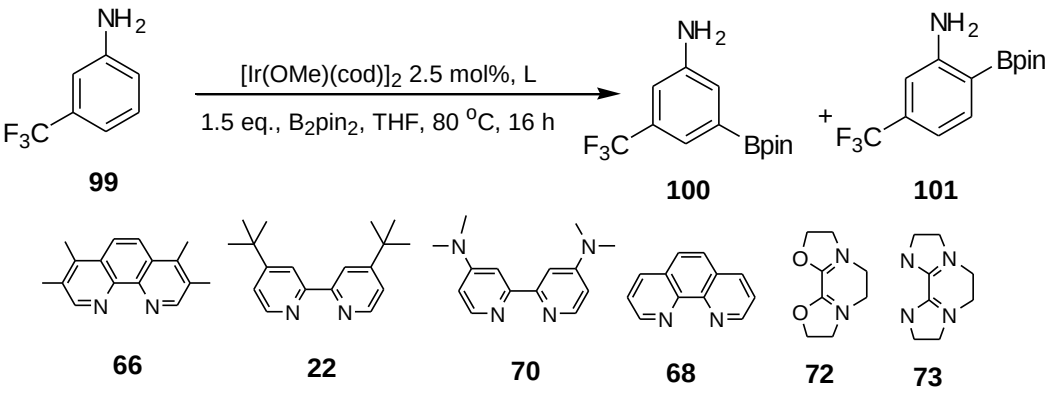
entry No	(L)	conv. (%)[a]	ratio[a] (97:98)
1	**78**	79	97:3
2	**79**	91	87:13
3	**80**	96	85:15
4	**81**	88	93:7
5	**82**	95	93:7
6	**83**	98	89:11

[a]rconversion and ratio determined by ^{1}H NMR

Table 13: Amine directed-C-H borylation[46]

The two ligands box **72** and diim **73** were used in the borylation of 3-tri-fluoromethylaniline **99** (**Table 14**).[40] They showed lower activity with the Ir-catalysts in the borylation of **99** compared with bipyridine derivatives (dtbpy **22** and dmabpy **70)** and [1,10]-phenanthroline derivatives (tmphen **66** and Phen **68**). Dmaby, dtbpy and tmphen ligands showed comparable activity in the borylation of **99** leading to the *meta* and *ortho* borylated products **100** and **101**. While box **72** and diim **73** showed the least activity with the Ir-catalyst. The selectivity of the borylation of aniline **99** was suggested to be due to hydrogen bonding of the N-H of the substrate with the boryl oxygen atom of the tris-boryl iridium complex, which would favor *ortho*-borylated

products. Using a polar solvent (THF), and high concentrations of B_2pin_2 might favour the formation of *meta*-borylated products.



99 **100** **101**

66 **22** **70** **68** **72** **73**

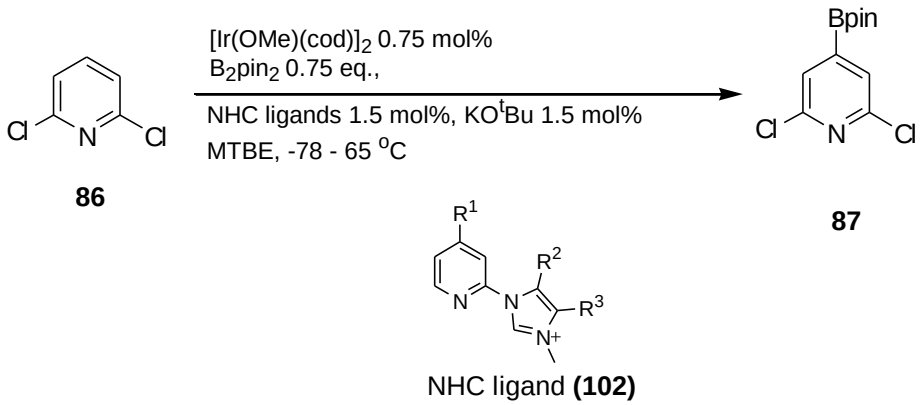
entry No	(L)	ratio[a] 100:101(m:o)	yield%
1	**66**	1.0:1.4	86
2	**22**	1.0:1.1	80
3	**70**	1.0:1.6	86
4	**68**	1.4:1.0	73
5	**72**	1.0:1.5	10
6	**73**	1.0:1.0	17

[a]ratio determined by ^{1}H NMR

Table 14: Borylation of 3-tri-fluoromethylaniline using different ligands[40]

1.1.4.4 Carbene Ligands

Another class of ligands which can be used in the borylation reactions are bidentate heterocyclic carbenes. Breinbauer and Peters reported a range of bidentate pyrido-NHC complexes which were used in the borylation of 1,3-di-chloropyridine **86** (**Scheme 12**).[49]



Scheme 12: Borylation of 1,3-di-chlorobenzene using carbenes ligands[49]

Although these ligands showed acceptable activity in the borylation of arenes, it was found that none of these carbene complexes give higher efficiency compared to dtbpy **22** with Ir-catalyst. Also Hermann *et al.* demonstrated a range of iridium mono- and bis-carbene complexes **103-108** that can be used in the borylation of arenes (**Figure 7**).[50] They showed that these complexes can be used in the borylation of benzene **31**, yielding only mono-borylated product with good yield, however these reactions need a higher temperature to 65 °C, which is not ideal due to the lower selectivity in the borylation reactions at elevated temperatures (**Table 15**).[50]

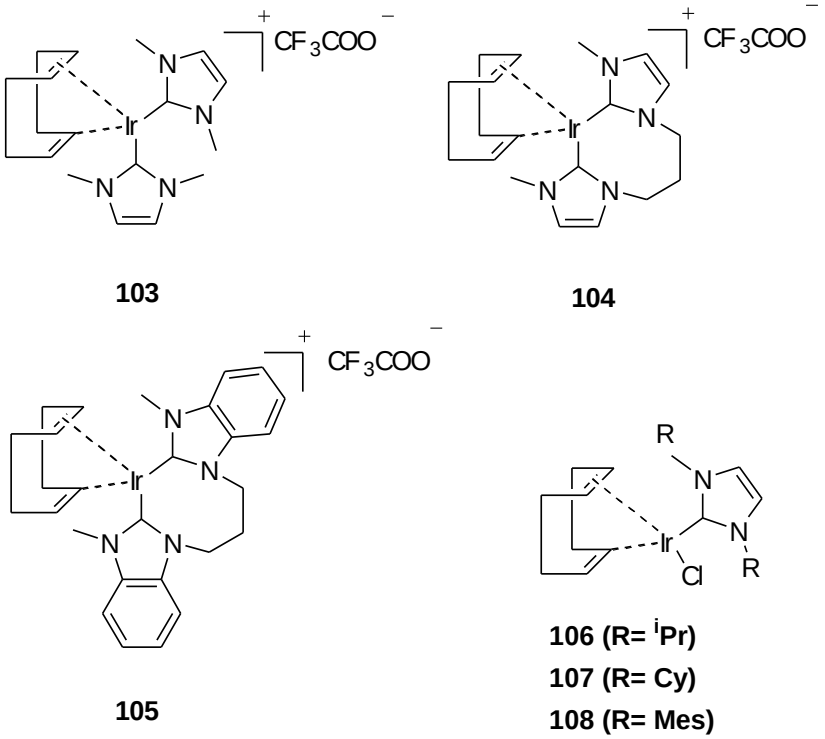
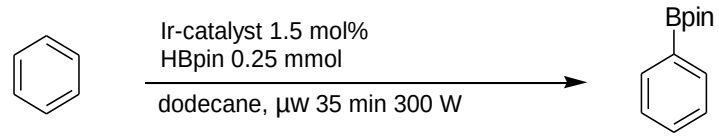


Figure 7: A range of iridium mono- and bis-NHC complexes[50]



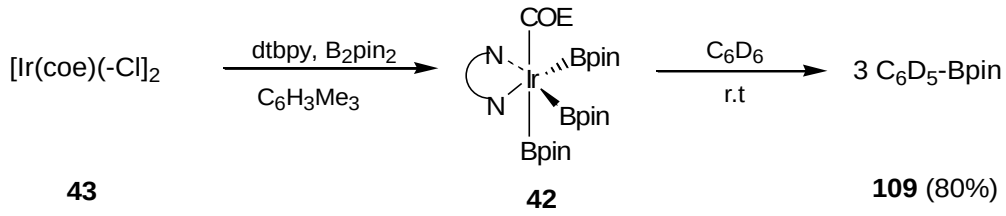
entry No	Ir-catalyst	Yield%
1	**103**	48
2	**104**	89
3[a]	**105**	87
4	**106**	72
5	**107**	68
6	**108**	75

[a]reaction time 1 h

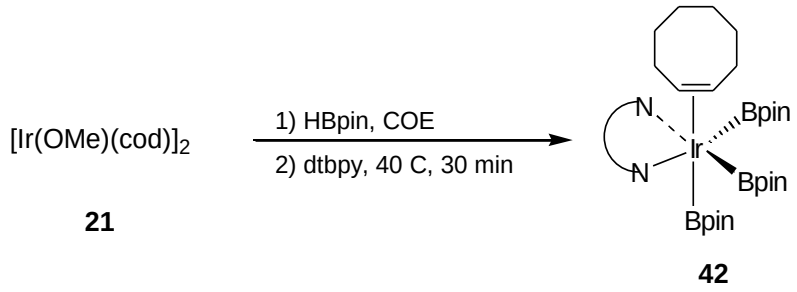
Table 15: Borylation of benzene using different iridium mono- and bis-NHC complexes[50]

1.1.5 Mechanism

A catalytic cycle for arene borylation with the Ir(Bpin)$_3$(dtbpy) **88A** complex has been suggested by Miyaura *et al*. (**Figure 8**).[29] The active 16 electron species **88A** is formed by reversible dissociation of COE from **42** and this conversion must take place before the borylation process.[51] The structure of **42** was confirmed by X-ray diffraction and studies have shown that the dissolution of the tris(boryl) species **42** in C_6D_6 at r.t gives 3 eq. of C_6D_5-Bpin **109** (**Scheme 13**). Collectively this evidence supports the idea that the tris (boryl) complex **42** is a key intermediate in borylation reactions.[29] Furthermore, in 2005 Hartwig *et al*. noted that complex **42** could be produced from the reaction of [Ir(OMe)(cod)]$_2$ **21** with HBpin (**Scheme 14**).[51]



Scheme 13: Dissociation of tris(boryl) species 42[29]



Scheme 14: Preparation of tris(boryl) species 42[51]

A plausible mechanistic pathway[29] commences with dissociation of COE from **42** to form the putative active Ir(III) complex **88A**. In the rate limiting step C-H activation of

the arene occurs to produce Ir(Ar)(H)(dtbpy)(Bpin)$_3$ **88B** through oxidative addition of the arene to the **88A**, followed by reductive elimination of Ar-Bpin **88C** to give Ir(H)(dtbpy)(Bpin)$_2$ **88D**. **88A** is then regenerated through oxidative addition of B_2pin_2 and reductive elimination of HBpin (**Figure 8**).

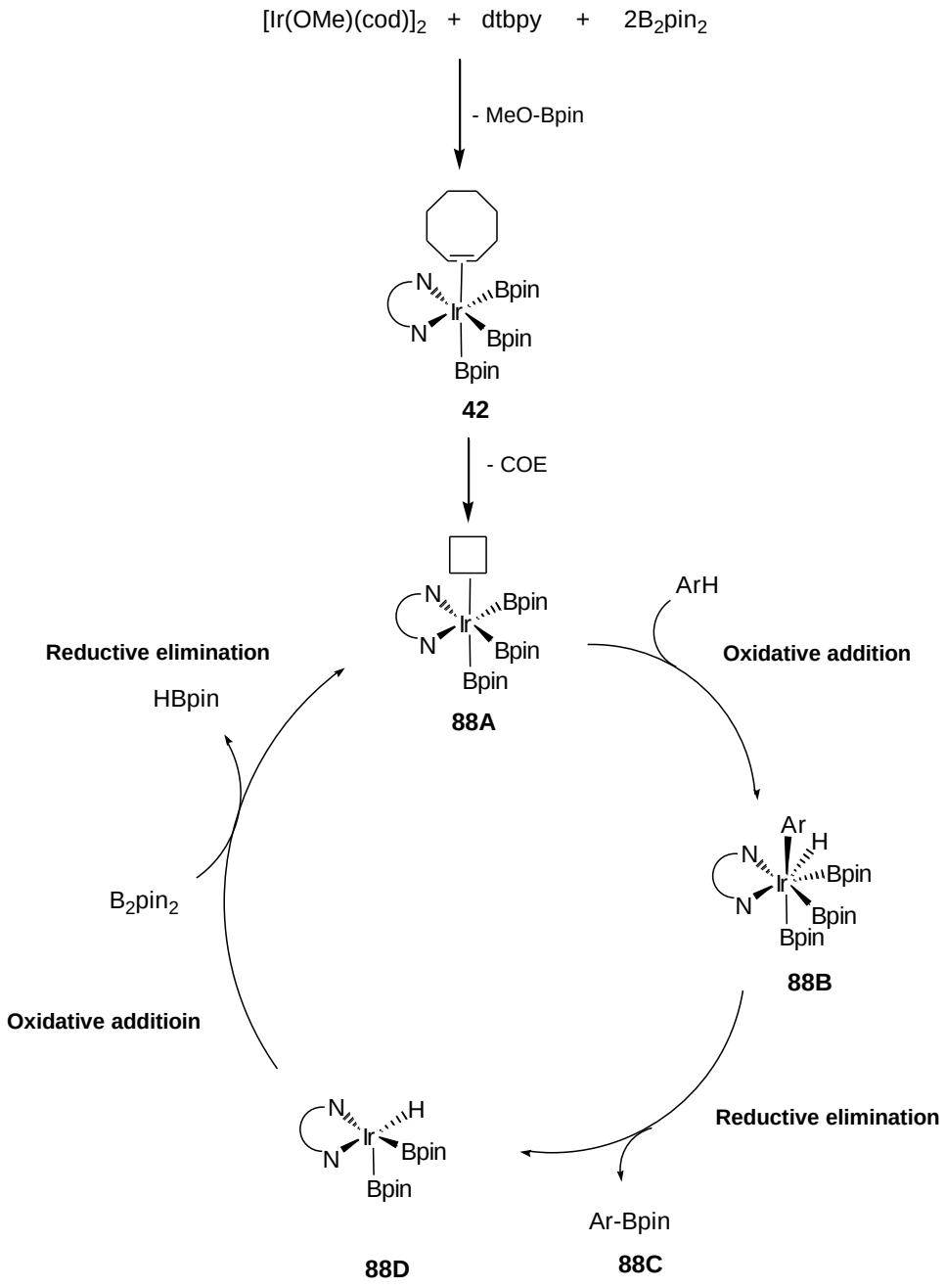


Figure 8: The proposed catalytic cycle[29]

This mechanism has been supported by computational results obtained by Sakaki *et al*. for the borylation of benzene.[52] It was also suggested that the tris(boryl) complex **88A** can be regenerated through oxidative addition of HBpin generated from the first cycle to the **88D** complex (**Figure 9**).[53]

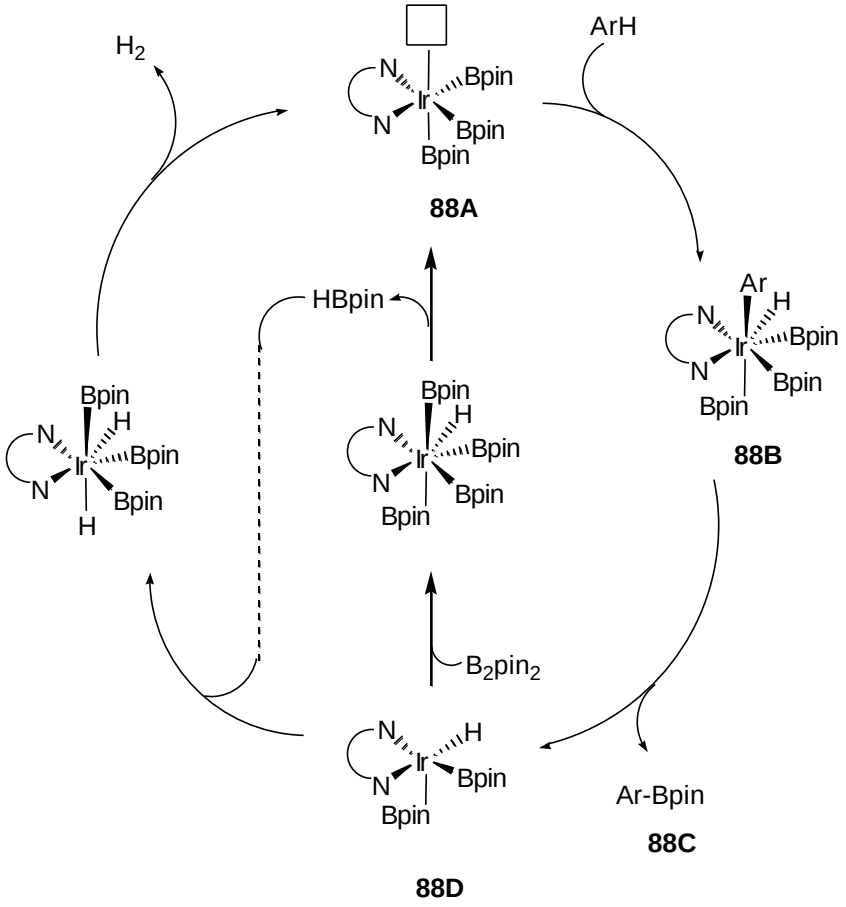
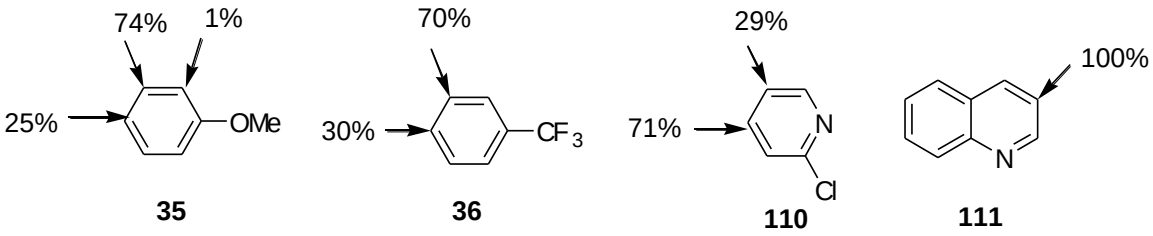


Figure 9: Proposed regeneration of the tris boryl species 88A[53]

1.1.6 Selectivity of Ir-catalyst for C-H borylation

$[Ir(OMe)(cod)]_2$ **21** ligated by dtbpy **22** is considered to be the most active type of catalyst for the borylation of arenes and heteroarenes.[54] Iridium catalysed C-H borylation is influenced by steric and electronic factors.[33,55] Previous studies have shown that the orientation of arenes and heteroarenes is influenced by steric

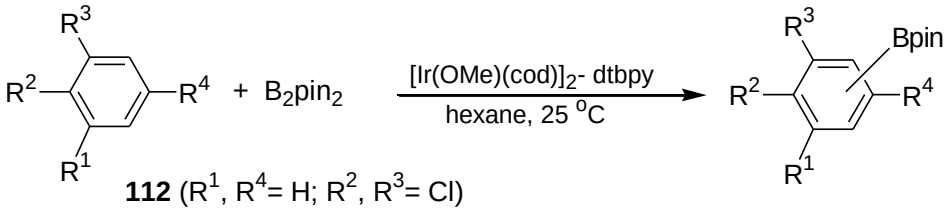
hindrance due to the high sensitivity of iridium catalysts towards steric effects.[33] This in turn affects the borylation process. However, for unsubstituted heteroarene C-H borylation, steric effects are largely absent. Mono-substituted aromatic C-H borylation at arenes that have electron-donating or electron-withdrawing groups gives a mixture of *para* and *meta* borylated products with the ratio determined by steric factors [29]. *Ortho* borylation in arenes or heteroarenes, such as anisole **35**, tri-fluromethylbenzene **36**, 2-chloropyridine **110** and quinoline **111**, is very poor and sometimes does not occur (**Figure 10**).



35 **36** **110** **111**

Figure 10: The orientations of arene and heteroarene C-H borylation[33]

In addition, arenes which bear symmetrical di-substituted groups on 1,2-positions and 1,4-positions give a single isomer[33] for example, 1,2-di-chlorobenzene **112** gives the 1,2,4 tri substituted product **115**. *Ortho* borylated product **116** can occur through borylation of symmetrical 1,4-di-chlorobenzene **113** (**Table 16**), however, a mixture of borylated products is formed on the borylation of 1,4-substituted arenes that have two different groups.[55] In addition, the borylation of 1,3-di-substituted arenes such as **114** takes place at the *meta* position (product **117**) even if the substituents are different or identical (**Table 16**).[33]



112 (R^1, R^4= H; R^2, R^3= Cl)
113 (R^1, R^3= H; R^2, R^4= Cl)
114 (R^1= Br, R^3= CN; R^2= H, R^4= H)

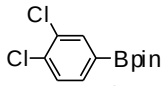
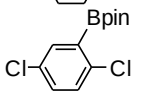
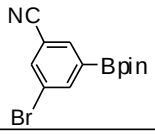
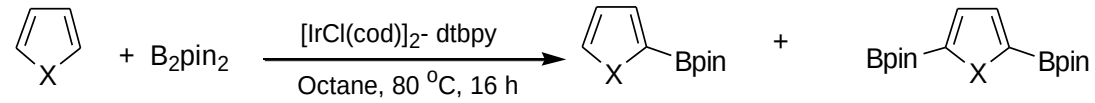
Comp No	R^1, R^2, R^3, R^4	R. time (h)	Ar-Bpin	Yield%
115	H, Cl, Cl, H	8		88
116	H, Cl, H, Cl	24		53
117	Br, H, CN, H	2		83

Table 16: Borylation di-substitutedbenzenes

1.1.7 Borylation of heteroarenes

The borylation of five-membered heteroarenes such as pyrrole, furan and thiophene, can also be catalyzed by iridium complexes.[32,56] With these substrates **118-120**, borylation takes place at the 2-position **121-123**.[57] 2,5-Bisborylated products **124-126**, however, are observed when the borylation of five-membered heteroarenes is achieved using excess of B_2pin_2 (**Table 17**).[57]

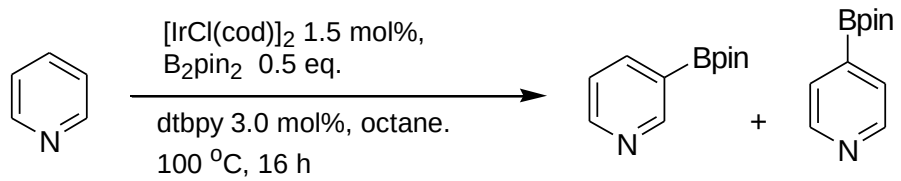


118 (X= O)
119 (X= NH)
120 (X= S)

(X)	B_2pin_2 (eq.)	Arene (eq.)	Prod No (A)	(A)Yield%	B_2pin_2 (eq.)	Arene (eq.)	Prod No (B)	(B) Yield%
O	1.0	10	**121**	83	1.1	1	**124**	71
NH	1.0	10	**122**	67	1.1	1	**125**	80
S	1.0	10	**123**	83	1.1	1	**126**	80

Table 17: Borylation of five-membered heteroarenes[57]

Furthermore, quinoline **111** and pyridine **127** should also be considered, as examples of the borylation of six-membered heteroarenes. Studies have found[58] that the borylation of unsubstituted pyridine **127** is less reactive than benzene **31**, and needs high reaction temperatures (100 °C), affording a *meta* and *para* borylated products **128** and **129** with a 2:1 ratio (**Scheme 15**).[32,58]This is due to the fact that the pyridyl nitrogen coordinates to the iridium catalyst blocking access to the position required for C-H activation.[58]



127

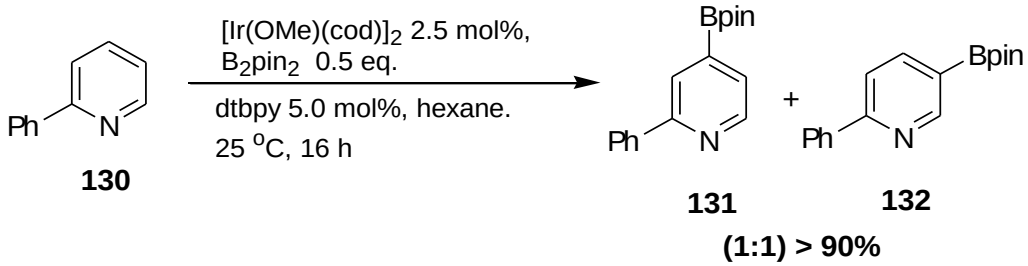
128 **129**

(2:1) 42%

Scheme 15: Borylation of pyridine compound[32,58]

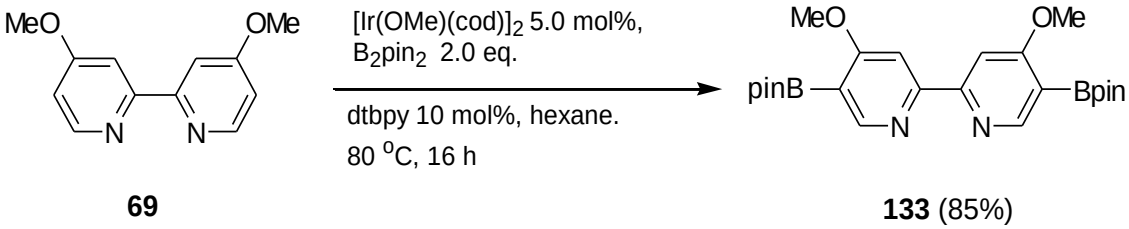
On the other hand, *ortho* substituents such as 2-phenylpyridine **130** give steric

inhibition of pyridyl nitrogen coordination allowing the efficient borylation of 2-phenyl pyridine. This yields a 1:1 mixture of 4- and 5-borylated products **131** and **132** (**Scheme 16**).[56]



Scheme 16: Borylation of a 2-substituted pyridine compound

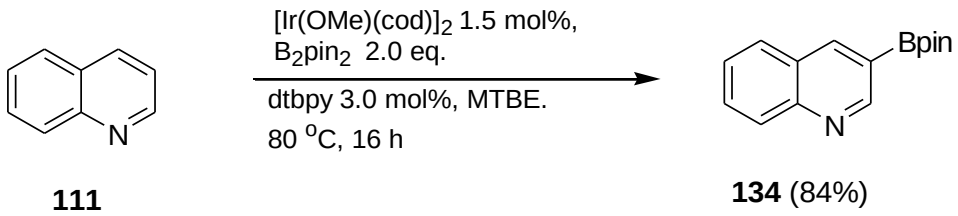
Through studying the inhibitory effects on the borylation of substituted heteroarenes,[58] it has been suggested that electronic effects possibly have a larger effect than steric hindrance. For example, the 5- and 5' borylated product **133** was produced through the borylation of **69** (**Scheme 17**).[56] However, this is almost certainly a substrate specific observation.



Scheme 17: Borylation of 4, 4´-di-methoxy-2,2´-bipyridine compound[56]

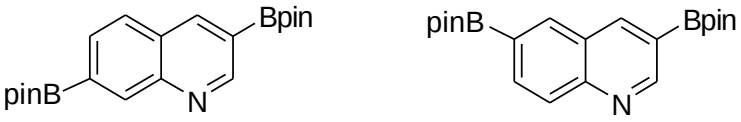
Another example of the issues affecting the borylation of heteroarenes comes from the use of quinoline **111**. Previous studies have shown that the borylation of **111** by

$[Ir(OMe)(cod)]_2$ **21** occurs in excellent yield (84%) at the 3-position **134** (**Scheme 18**),[59] while increasing the amount of B_2pin_2 leads to bis-borylated products **135** and **136** (**Figure 11**) in a 50:50 ratio.



111 **134** (84%)

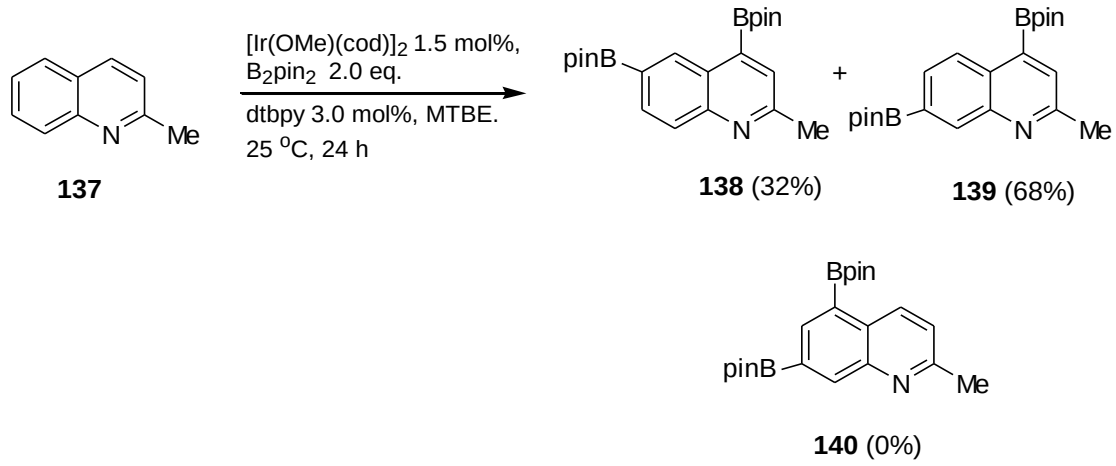
Scheme 18: Borylation of quinoline[59]



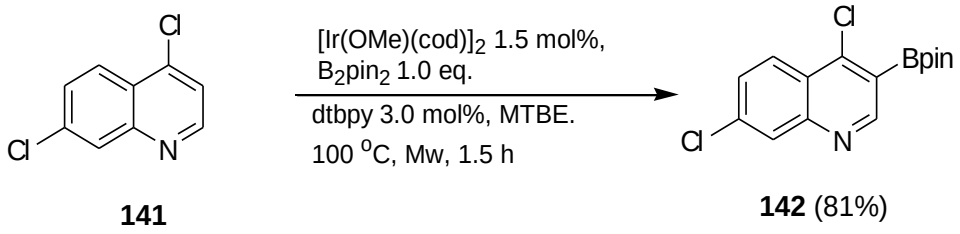
135 **136**

Figure 11: Bis-borylated quinoline[59]

In addition, the blocking of the 2-position on quinoline by any group such as 2-methylquinoline **137** leads to bis-borylated product at 4,6 (**138**) and 4,7 (**139**) with a small amount at 5,7 (**140**) positions;[58] this is due to steric inhibition of pyridyl nitrogen coordination (**Scheme 19**). Furthermore, the borylation of the di-substituted quinoline at 4- and 7- positions **141** leads to mono-borylated product at the 3-position **142** (**Scheme 20**).



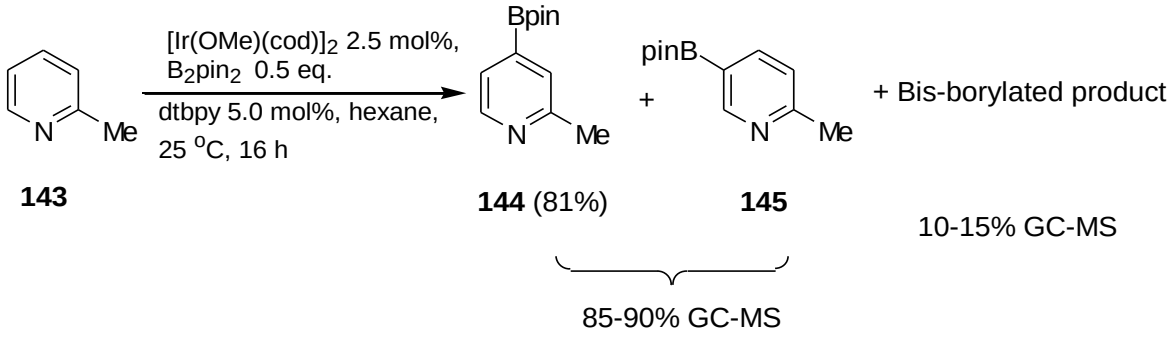
Scheme 19: Borylation of 2-substituted quinoline[58]



Scheme 20: Borylation of 4,7-di-chloroquinoline[58]

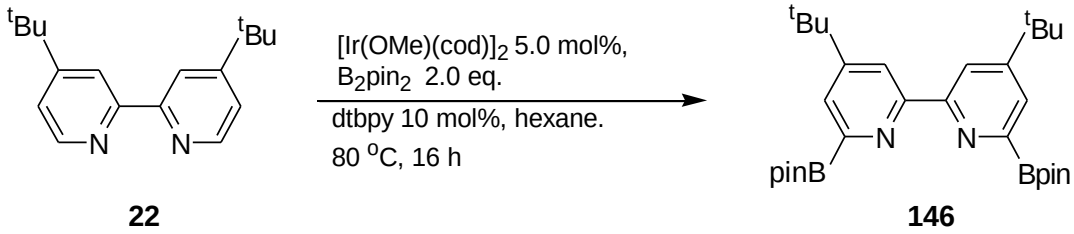
1.1.8 Previous work in the group (application of pyridines and quinolines)

The borylation of heteroarenes such as quinoline **111** and pyridine **127** were investigated by previous members of the research group. Quinoline **111** as a substrate showed more reactivity in the borylation reaction than pyridine **127** (**Section 1.1.5, Scheme 15, Scheme 18**). Mkhalid has studied the electronic and steric effects on heteroarene C-H borylation. It was found that blocking the 2-position on pyridine such as 2-methylpyridine **143** leads to good conversion in borylation reaction at 4- and 5-positions **144** and **145** (**Scheme 21**).[57]



Scheme 21: Borylation of 2-methylpyridine[57]

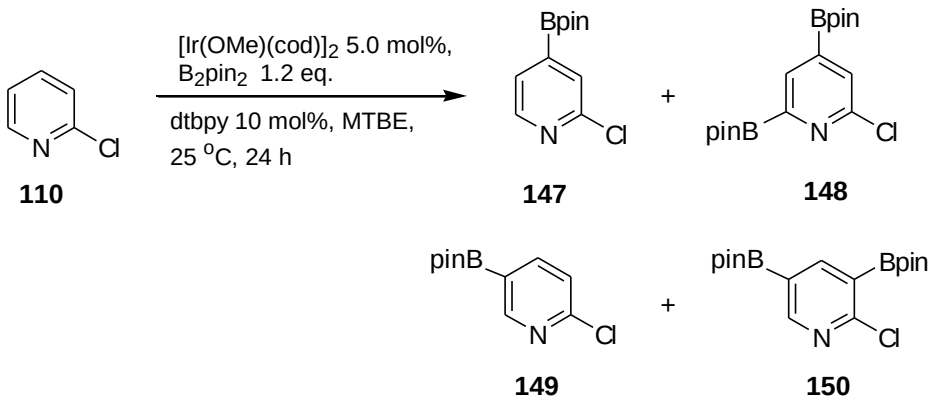
This researcher also demonstrated that the dtbpy **22** can be borylated by using stoichiometric dtbpy **22** giving a bis-borylated product at the 6- and 6'-positions **146** (**Scheme 22**).



Scheme 22: Borylation of a 4, 4'-di-tert-butyl 2,2´-bipyridine compound[57]

As mentioned in **Section 1.1.5** (**Scheme 17**) that while 5- and 5' borylated product was produced through the borylation of **69** from the results above, it was found that the selectivity of iridium C-H borylation of pyridines more commonly depends on steric hindrance rather than electronic effects. In addition, Tajuddin has studied the selectivity of iridium C-H borylation on variety of substituted pyridines.[10] The borylation of 2-chloropyridine **110** afforded 6-borylated product **148** after initial

borylation at the 4-position **147** due to the electronic effects of pyridyl nitrogen (**Scheme 23**).



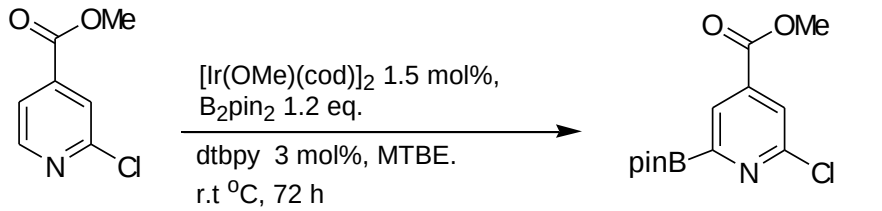
110 **147** **148** **149** **150**

Conv (%) GC-MS ratio (147:148:149:150)

100 **29:40:26:5**

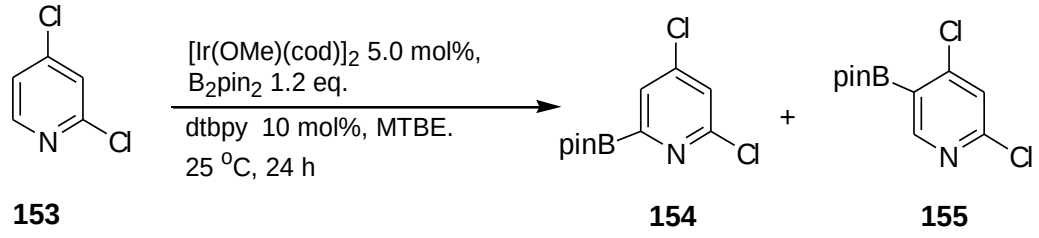
Scheme 23: Borylation of 2-chloropyridine[10]

It was found that blocking the 2- and 4-positions on pyridine such as methyl-2-chloroisonicotinate **151** led to *ortho* borylated product **152** (**Scheme 24**). This meant that the borylation *alpha* to the pyridyl nitrogen occurred as a result of the steric effects of the ester group at the 4-position. On the other hand, a mixture of 5- and 6-borylated products **154** and **155** were observed when an ester group at the 4-position was replaced by a chlorine atom **153** (**Scheme 25**).



151 **152 (73%) ^{1}H NMR**

Scheme 24: Borylation of a 2,4-di-substituted pyridine[10]

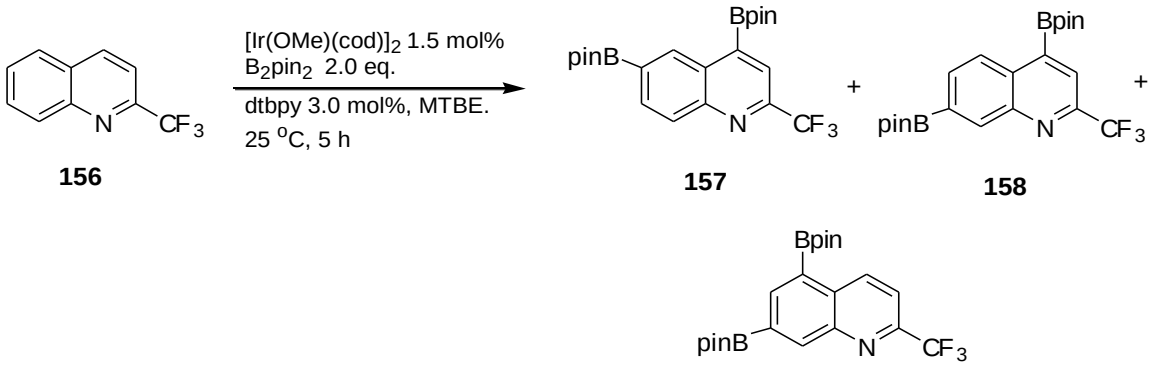


153 **154** **155**

(95%) conversion

Scheme 25: Borylation of 2,4 di-chloropyridine[10]

Tajuddin has observed that the borylation of 2-CF_3-substituted quinoline **156** giving a mixture of bis borylated products **157-159** (**Scheme 26**).



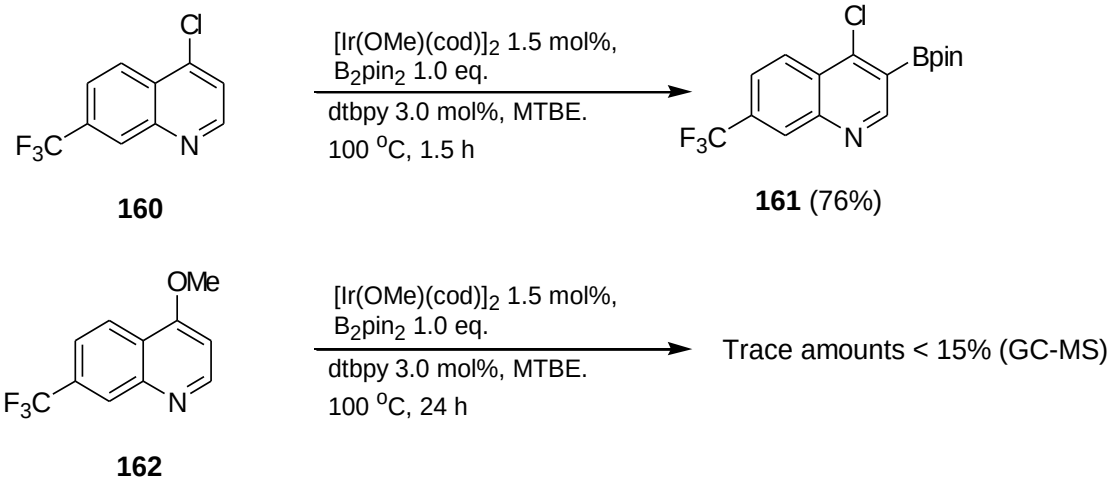
156 **157** **158**

159

Conv (%)	GC-MS ratio (157:158:159)
> 90	42:51:7

Scheme 26: Borylation of a 2-substituted quinoline[10]

Harrisson[21] also investigated the borylation of quinoline derivatives. It was found that the borylation of 4-Cl-7-CF_3 substituted quinoline **160** gives only mono borylated product **161** depending on the functional groups on quinoline. Different results were found when the chlorine atom at the 4-position was replaced by a methoxy group **162** (**Scheme 27**). These results are similar to those produced from the borylation of dtbpy **22** and 2-chloroisonicotinate **151**.

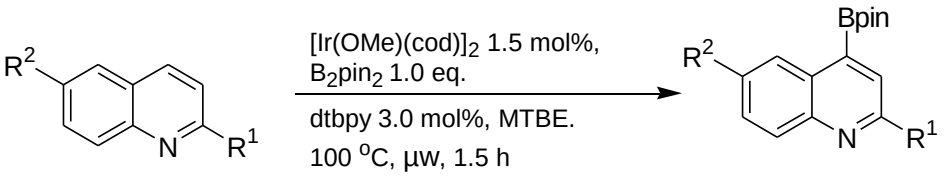


160 **161** (76%)

162

Scheme 27: Borylation of 4,7-di-substituted quinolines[21]

It was found that 4-borylated products **165** and **166** were observed during the borylation of 2,6-di-substituted quinolines **163** and **164** (**Table 18**).

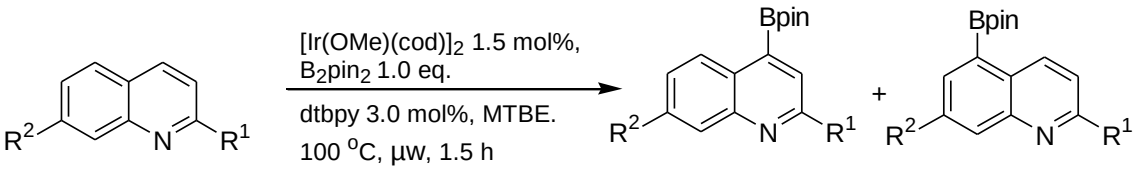


163 (R^1= Me, R^2= OMe)
164 (R^1= Me, R^2= Cl)

Prod No	R^1, R^2	Yield%
165	Me, OMe	76
166	Me, Cl	79

Table 18: Borylation of 2,6-di-substituted quinoline[21]

Borylation of 2,7-di-substituted quinolines **167** and **168** gives mixtures of 4 and 5-borylated products **169** and **170** as observed by GC-MS (**Table 19**).



167 (R^1= Me, R^2= OMe)
168 (R^1= Me, R^2= Cl)

Prod No	R^1, R^2	Conv[a] %	Ratio[a] (A:B)	Yield%
169	Me, OMe	> 95	90:10	nd
170	Me, Cl	92	65:35	61[b]

[a]conversion and ratio determined by GC-MS; [b]minor isomer isolated in 11% yield

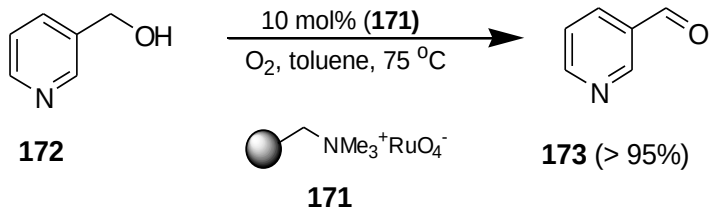
Table 19: Borylation of a 2,7-di-substituted quinoline[21]

Iridium C-H borylation of heteroaromatics such as quinolines and pyridines derivatives is more complicated than carbocyclic aromatics due to the electronic effects and challenges remain for future study.

1.2 Polymer supported catalysis

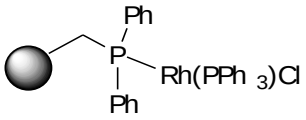
Polymer supported catalysis is an important area that has been investigated by many chemists. A large number of reviews on solid-supported catalysts have been published over the past few years.[60-64]For example Janda *et al.* recently reviewed polymer supported catalysts which can be used in different organic reactions such as oxidation, reduction and transition metal-catalysed reactions.[60] The use of polymer supported catalysts helps the isolation of product, allows recycling of the expensive catalysts by simple filtration, increases the selectivity of the reactions and enables reuse the catalysts for further reactions.[60,65] These criteria can be achieved by polymer supported ligands. This means that the ligands are a main key to achieving the desired goal in the polymer supported catalysis. Supported ligands can be prepared by the

reaction of a simple functionalized polymer with a derivative of the desired ligand.[66] Ley and co-workers prepared polymer supported perruthenate catalyst **171** which could be used to oxidise a primary alcohol **172** to aldehyde **173**. This catalyst was prepared using tetra-propylammonium perruthenate TPAP with Amberlyst A-26 resin (**Scheme 28**).[67] This catalyst showed selectivity for only primary alcohols.



Scheme 28: Reduction of primary alcohol using 171[67]

Wilkinson's catalyst **174** is used for the hydrogenation of alkenes. This catalyst was prepared by phosphine bound to polystyrene and complexed to rhodium (I) chloride (**Figure 12**).[68]



174

Figure 12: Wilkinson's catalyst 174[68]

Catalyst **174** can be recovered and re-used for 10 cycles without loss in catalytic activity. For the reduction of ketones, the catalyst **175** was prepared by adding HBr in acetone to a mixture of di-phosphine polymer and Ru(cod)(bis-methallyl) (**Figure 13**).[60,69] This catalyst showed good activity in the formation of β-hydroxy ester **177**

from β-keto ester **176** (**Scheme 29**).[60] Additionally, this catalyst showed selectivity for the asymmetric hydrogenation of the olefin in amino acid **178** to give amino acid **179** (**Scheme 30**).[60]

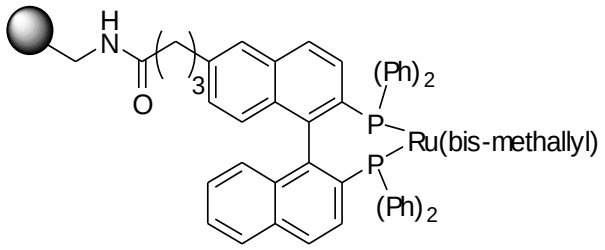
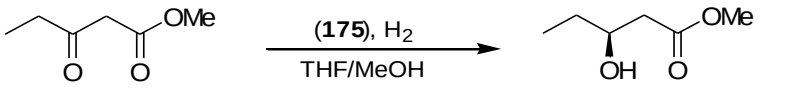
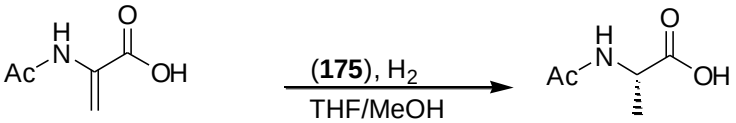


Figure 13: Ru(cod)(bis-methallyl) catalyst 175[60,69]



176 **177** (99% yield, 99% ee)

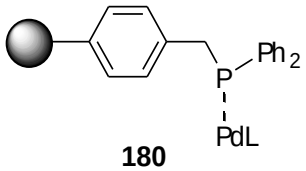
Scheme 29: Reduction of β, keto ester using 175[60]



178 **179** (90% yield, 64% ee)

Scheme 30: Hydrogenation of the olefin in amino acid using 175[60]

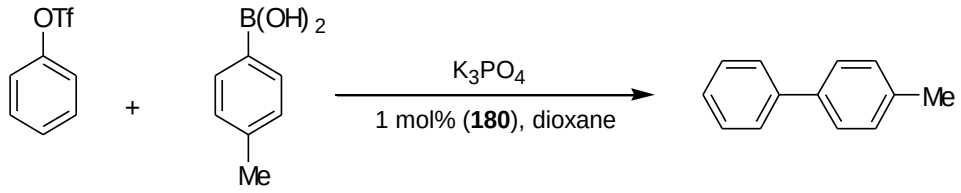
For transition metal catalysts, many different polymers were used in polymer supported catalysis. The most common polymer is polystyrene.[70] For example, catalyst **180** was prepared by the reaction of lithium di-phenylphosphide with chloromethylpolystyrene. The resulting product was then reacted with a Pd source (**Figure 14**).[60]



180

Figure 14: Polystyrene supported palladium catalyst 180[60]

This catalyst showed good activity through the coupling of ArOTf **181** with Ar-B(OH)$_2$ **182** to form bi-aryl **183** in Suzuki cross-coupling reactions (**Scheme 31**).[71]



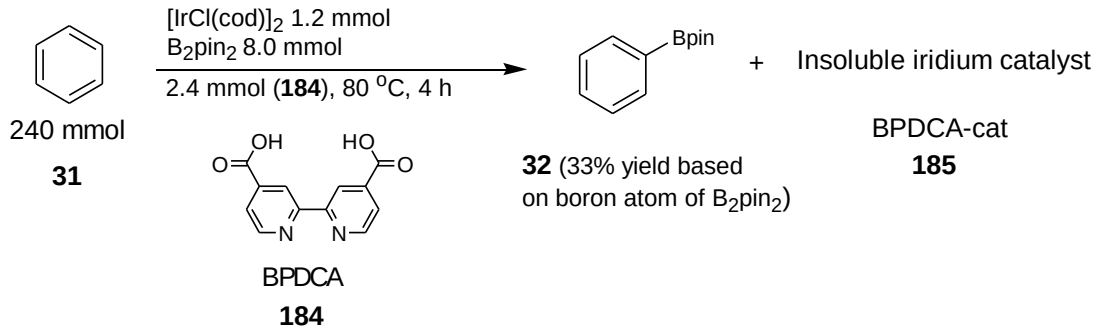
181 **182** **183** (90%)

Scheme 31: Suzuki Miyaura cross-coupling using 180[71]

1.3 Polymer supported iridium catalyst

Due to its high usage in many catalytic applications, iridium is predicted to become unavailable in the near future. One potential solution is to prepare heterogeneous catalytic complexes. The big challenge is, if it is possible, to recover and re-use the catalyst for further reactions without losing catalytic activity. Furthermore, the catalysts may not be air stable and may decompose over time. In the past years, different ligands were used to generate the catalytic borylation complex for arenes. Among these ligands, 2,2'-bipyridine derivatives were found to be the best class for generating the active iridium catalyst in the borylation of arenes.[29,47] In 2007 Zhu *et al.* prepared ionic liquid-stabilised iridium complexes for the borylation of arenes.[72,73] This iridium complex could be re-used six times. However, recovery of the catalytic complex

was difficult and the borylated product needed to be isolated by distillation.[74] In 2009 Nishida *et al.* used 2,2'-bipyridine-4,4'-di-carboxylic acid **184** as a ligand with $[Ir(cod)Cl]_2$ **37** in presence of B_2pin_2 for the borylation of benzene **31** (**Scheme 32**).[75] This borylation led to the generation of a heterogenous iridium catalyst (BPDCA-cat) **185** which could be recovered and re-used 10 times. Unfortunately, the heterogeneous iridium complex was oxidised by air.



Scheme 32: Preparation of heterogeneous Ir-BPDCA-cat 185[75]

Sawamura *et al.* used a silica supported iridium catalyst in the directed-*ortho* borylation of aromatic ester derivatives (**Figure 15**).[41,42,76]Although the silica supported iridium catalyst **186** showed good activity in the borylation reaction, the isolation of the Ir-complex was unsuccessful. This was due to instability of the supported iridium complex to air.[43]

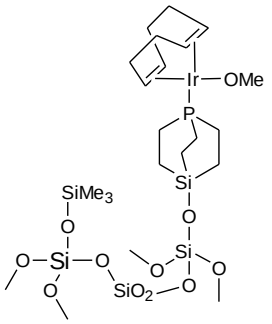
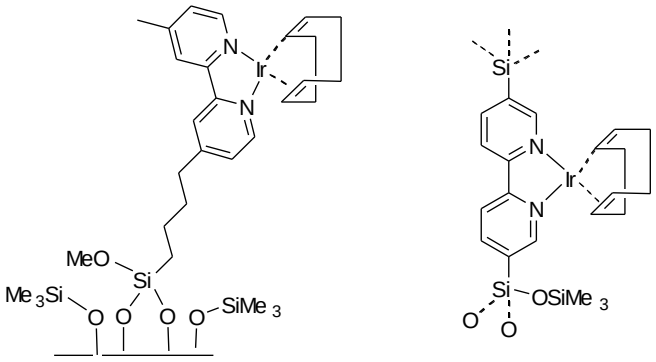


Figure 15: Silica-SMAP-Ir-Cat 186[42]

In 2014, Jones *et al.*[74] and Copéret *et al*.[77] also prepared a silica supported iridium catalyst **187** and **188** (**Figure 16**). These supported iridium catalysts were generated using bipyridine-SBA-15 or bipyridine-PMO as the supported bipyridine ligand with $[Ir(OMe)(cod)]_2$ **21** and B_2pin_2. These heterogeneous iridium complexes can be recovered and re-used several times with a slight loss in the activity of the catalytic borylation. Additionally these catalyst showed good activity in the borylation of arenes and had tolerance for a wide variety of electron-withdrawing and electron-donating groups.

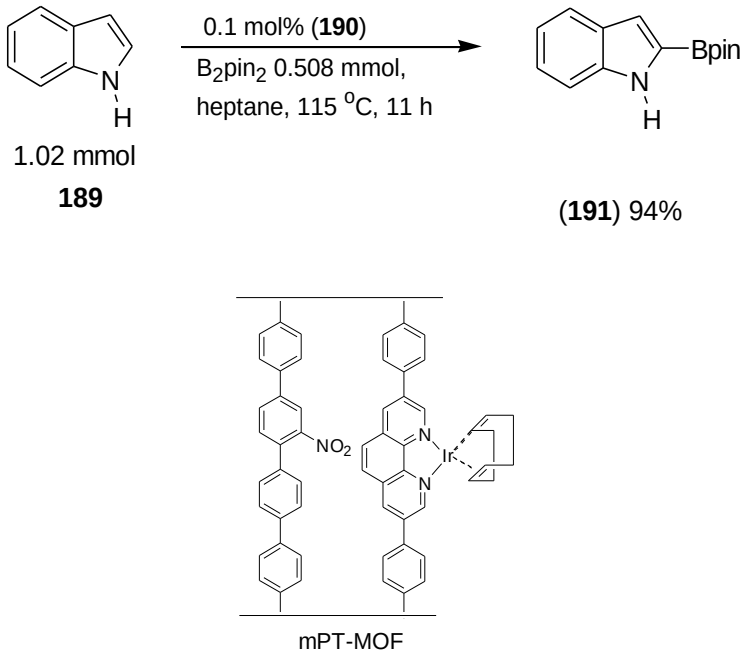


Ir-SBA-15-cat **(187)**

Ir-PMO-cat **(188)**

Figure 16: Silica supported iridium catalysts[74,77]

Recently Lin *et al.*[78] were prepared a range of MOF-Ir complexes for the borylation of arenes. These MOF-Ir complexes showed good activity in the borylation of arenes. It was found that with a loading of 0.5 mol% of MOF-Ir the catalyst could be recovered and re-used 10 times. Indole **189** can be borylated using mPT-MOF-Ir **190** in the presence of boron source such as B_2pin_2 to afford the 2-borylated product **191** (**Scheme 33**).



Scheme 33: Borylation of indole using mPT-MOF 190[78]

1.4 In conclusion

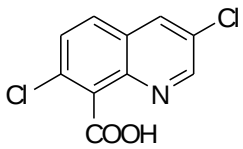
Ir-catalysed C-H borylation is a powerful strategy for arene functionalization. Ligands play a big role in the success of the borylation reactions. Many different ligands were used in the borylation of arenes, and bipyridine and tmphen ligands were found to be optimal with an Ir-catalyst to generate the active catalyatic species $Ir(Bpin)_3$ ligand. These ligands were used in the borylation of specific substrates, however the design of ligands affording high regioselectivity in the borylation reaction remains a significant challenge.

Polymer supported catalysts can be applied to many different reactions in organic chemistry. For example silica supported iridium catalysts **187** and **188** showed good activity in the borylation of arenes, enabling recovery and re-use for further borylation reactions by simple filtration. Bipyridines and tmphen were found to be the most active class of ligands in this process, allowing easy attachement to a polymer.

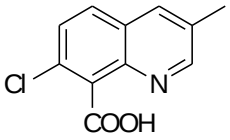
Preparation of ligands with suitable linkers remains a challenge in this area, which shall be discussed in chapters 3 and 5.

1.5 Aims and Objectives

As discussed in Chapter 1, arylboronate esters have many applications in modern chemistry and CH borylation is arguably the best way to prepare these important reagents. The work undertaken in this thesis is comprised of three discrete areas both enhancing the efficiency of the borylation reaction and applying it to new heterocyclic systems and synthesis. Quinoline derivatives have been widely exploited as novel herbicides (**Figure 17**)[79] and in a different biological project within the group, access to a series of 4,5 dihydroxy quinolones was required. It was anticipated that these could be obtained via borylation and oxidation (**Chapter 2**, **Section 2.1**, **Figure 18**). Previous studies within our group had addressed the borylation of 2,7- and 4,7-substituted quinolines (**Chapter 1**, **Section 1.1.8**, **Table 19**, **Scheme 27**) and the selectivity was found to be influenced by electronic effects. It was therefore of interest to prepare 2-aryl quinoline and quinolone derivatives and borylated highly substituted 2-arylquinoline derivatives to explore the selectivity of this borylation as a means of accessing the desired substituted quinolones. This work is discussed in detail in Chapter 2.



Quinclorac



Quinmerac

Figure 17: Quinoline derivatives as novel herbicides[79]

In a related project in the group the regiochemistry of the borylation of pyridines had been explored and it had been shown that this required a substituent in the 2 position.

If this group was sufficiently electron-withdrawing then it was possible to observe the 6-boryl pyridine. Since pyridines represent a fundamental scaffold for pharmaceuticals and agrochemicals efficient ways to synthesise highly substituted derivatives are an important synthetic goal. By using suitably 2-halo-4-substituted pyridines, it was proposed that a borylation cross-coupling-S_NAr strategy (**Section 4.1**, **Figure 29**) could be used in the preparation of 2,4,6-substituted pyridine derivatives. The chemistry undertaken to explore this concept is described in chapter 4.

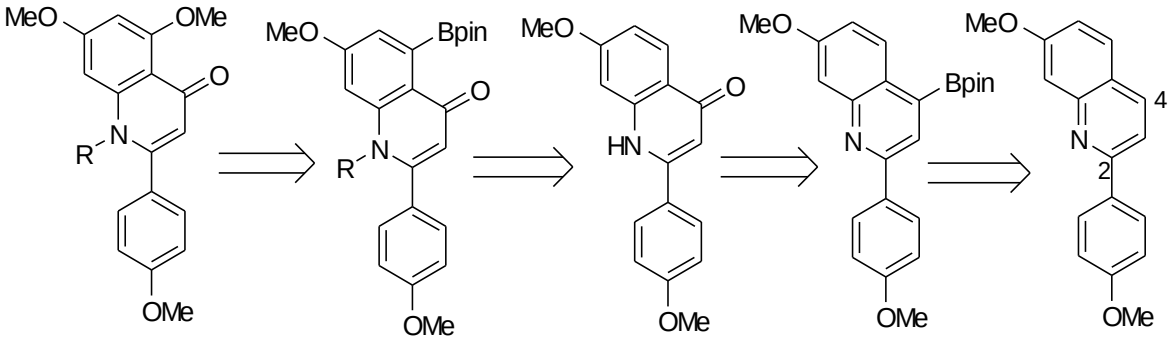
The final aim of this project was to explore the preparation of a polymer supported iridium catalyst. Whilst C-H borylation is probably the optimal method for the synthesis of aryl boronate esters the cost of iridium is problematic. Moreover, iridium resources are finite and are likely to run out in the future. The preparation of heterogeneous iridium catalysts could help to overcome this problem as the catalyst could then be recovered by simple filtration and then re-used for further reactions. In order to achieve this a suitable ligand, which could be attached to a polymer via a linker and then used to immobilize the iridium catalyst needs to be identified. It was envisaged that existing bipyridine and 1,10-phenanthroline ligands could be modified to incorporate a suitable linker. These could then be evaluated and compared to the commercially available equivalent homogeneous ligands for catalytic efficiency and recoverability. This work is described in Chapter 3 and 5.

Chapter 2

2 Borylation of quinolines

2.1 Introduction

In previous work carried out within the group the borylation of 2-methylpyridine had been shown to occur exclusively in the heteroaromatic ring (**Section 1.1.8, Scheme 21**). In a related study the selectivity of the borylation of several azinyl derivatives had been studied.[80] In particular the borylation of quinoline derivatives had provided insights into an electronic influence on selectivity (**Section 1.1.8, Table 19**). As means of gaining experience in borylation methodology an initial goal of the project was to prepare 2-arylquinoline derivatives and explore the selectivity of the borylation of these compounds. In particular 2-arylquinolone product **193** was of interest within the group as precursors for novel herbicides[81] and the synthesis of this represented a second objective in this project. It was anticipated that this might arise from the regioselective borylation of quinolone **192B**, which in turn might be prepared via the borylation of a 2 –aryl quinoline at C-4 (**Figure 18**).



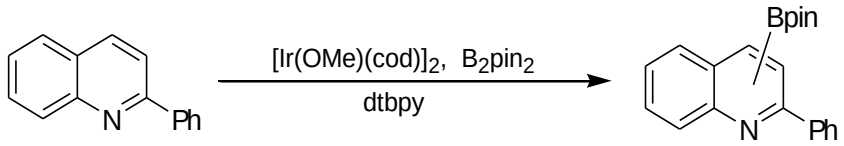
193 **192B**

Figure 18: Retrosynthetic analysis of the desired 2-aryl-quinolone

2.1.1 Borylation of 2-arylquinoline derivatives

2.1.1.1 Borylation of 2-phenylquinoline

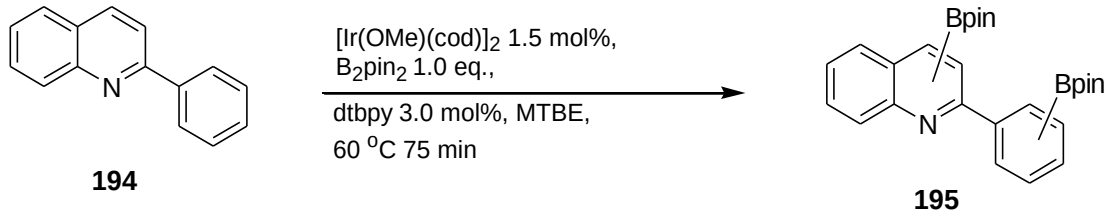
Initial experiments were undertaken using 2-phenylquinoline **194** (**Scheme 34**) to explore the intrinsic regioselectivity of the reaction. **194** was borylated using the catalytic species **88A** prepared in situ from the reaction of $[Ir(OMe)(cod)]_2$ **21**, dtbpy **22** and B_2pin_2.



194 **195**

Scheme 34: Borylation of 2-phenylquinoline derivatives

Following the addition of all of the reagents, the reaction mixture was heated at 60 °C in a μW for 75 min. This afforded a complex mixture of mono- and bis-borylated products **195** with a small amount of unreacted starting material, 12% according to GC-MS trace (**Scheme 35**). More detailed analysis was achieved by GC-MS integrating the M^+ peaks at Rt = 26.0-26.8 min; 31.7-36.9 min with *m/z* = 331 ($[MH]^+$) and 457 ($[MH]^+$), respectively. This indicated that the crude mixture contained 5 mono and 6 bis-borylated products in a 57 % (19:6:15:12:5): 31% (5:5:6:10:3:2) ratio.



194 **195**

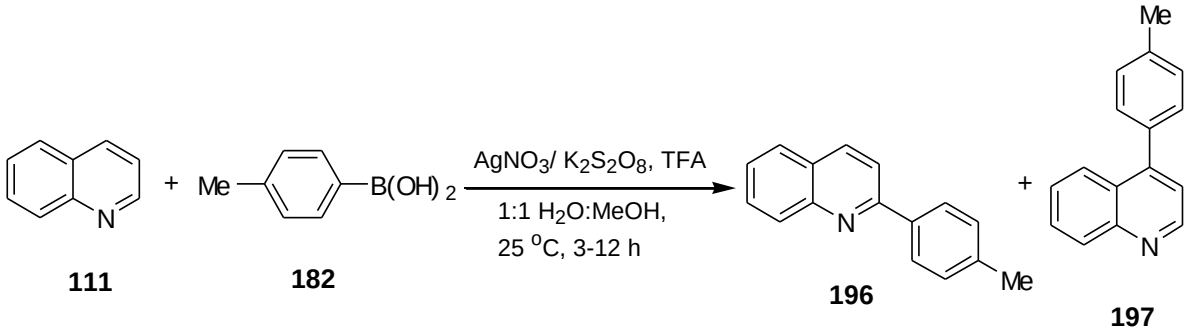
conv (%) GC-MS	(mono):(bis)
88	57:31

Scheme 35: Borylation of 2-phenylquinoline

Attempts to enhance the selectivity by carrying out the reaction at room temperature for 21 h were not successful and gave a similar result. This level of borylation implied that in contrast to 2-methylquinoline **137**, reaction at the phenyl substituent must be occurring. To prevent this unwanted reaction the introduction of substituents in the phenyl ring was proposed. With this in mind the immediate objective of the project was the synthesis of suitable 2-arylquinolines and this is discussed in the next section.

2.1.2 Synthesis of 2-(aryl-substitution)-quinolines derivatives

As discussed above a route to 2-arylquinolines was needed. A survey of the literature revealed a recent report by Baran[82] in which quinoline **111** could be substituted at the 2-position using arylboronic acid **182** in presence of $AgNO_3$, $K_2S_2O_8$ and TFA (**Scheme 36**). Importantly quinolines appeared to be viable in this transformation. This approach would allow a range of different 2-arylquinolines to be easily prepared and was therefore selected for exploration.

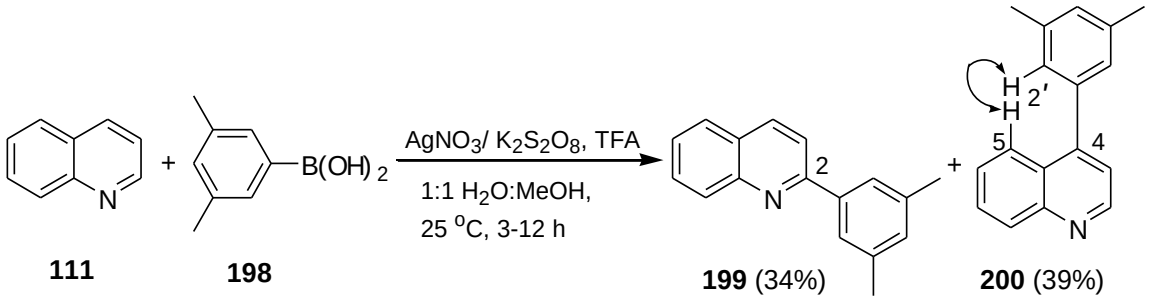


111 **182** **196** **197**

61% (C2:C4 2:1)

Scheme 36: Baran's preparation of 196 and 197[82]

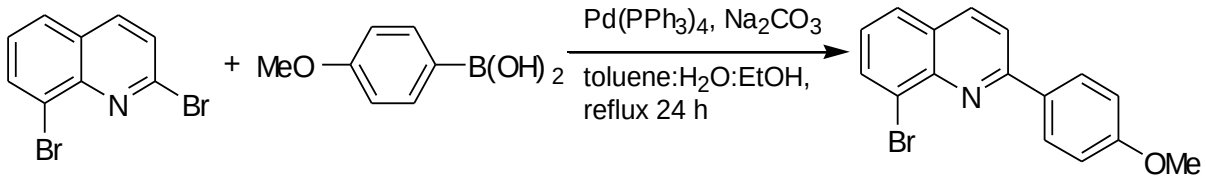
Following the Baran precedent, a mixture of quinoline **111**, 3,5-di-methylphenylboronic acid **198**, $AgNO_3$ and $K_2S_2O_8$ in TFA were stirred at 25 °C for 12 h (**Scheme 37**). After work up, analysis of the crude reaction mixture by GC-MS revealed the presence of a mixture of two mono substituted quinolines **199** and **200**, as revealed by the presence of peaks with Rt = 11.1 and 12.0 min both with *m/z* = 233 ($[MH]^+$). Following chromatography, the desired 2- and 4-arylquinoline derivatives (**199** and **200**, respectively) could be isolated with yields of 34% and 39% respectively. Confirmation of the proposed structures was obtained from the ^{1}H NMR spectra. Compound **199** shows characteristic methyl signals for the xylyl group at δ = 2.5 and lacks a characteristic quinoline 2-H signal at δ = 8.9 ppm whereas compound **200** still has a signal for the 2-H at δ = 8.9. For compound **200**, substitution at C-4 was confirmed by a NOESY correlation between 2'-H and 5-H.



111 **198** **199** (34%) **200** (39%)

Scheme 37: Preparation of 199 and 200

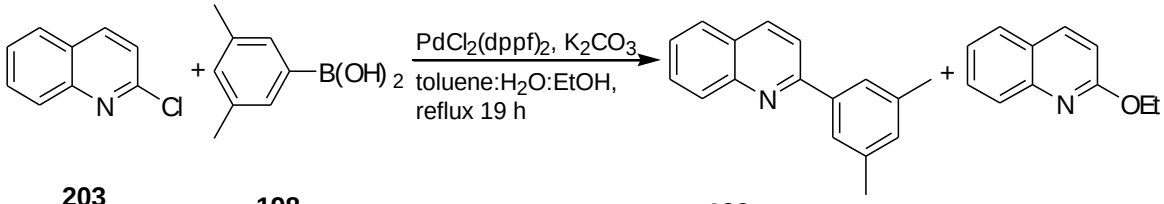
The poor selectivity of the reaction coupled with the difficult column chromatography made this process an inefficient method for the preparation of the target compound. Consequently an alternative pathway was sought. A survey of the literature revealed that the 2-arylquinoline **202** can also be formed from the corresponding 2-bromoquinoline **201** using $Pd(PPh_3)_4$ through the Suzuki-Miyaura cross-coupling reaction (**Scheme 38**).[83]



201 **5** **202 (84%)**

Scheme 38: Preparation of a 2-arylquinoline derivatives[83]

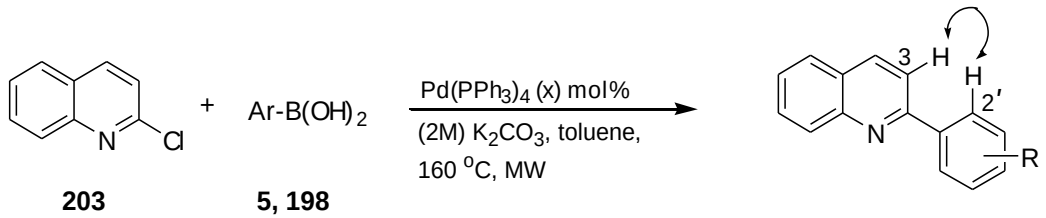
The conditions above were first tested using 2-chloroquinoline **203,** Ar-$B(OH)_2$ **198,** and $PdCl_2(dppf)_2$ (**Scheme 39**). This led to the desired product **199** along with 2-ethoxyquinoline **204** as observed by GC-MS analysis. Formation of product **204** might be due to the ethanol in the reaction mixture. Although this method gave complete conversion, purification by column chromatography was very difficult and the desired product **199** could not be isolated.



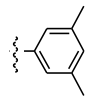
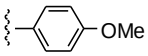
203 **198** **199** **204**

Scheme 39: Preparation of 2-(3,5-di-methylphenyl)-quinoline

To avoid this problem the reaction was then attempted using a toluene-water solvent mixture.[84] Pleasingly, under these conditions, reaction of **203** with **5** and **198** afforded the desired 2-aryl quinolines **199** and **205** in 69-85% yields respectively (**Table 20**).



203 **5, 198**

Comp No	Ar	Pd mol%	reaction time (s)	Rt min: (m/z)[a]	Yield%
199		10	10	12.0: (233 $[MH]^+$)	69
205		5	60	12.7: (235 $[MH]^+$)	85

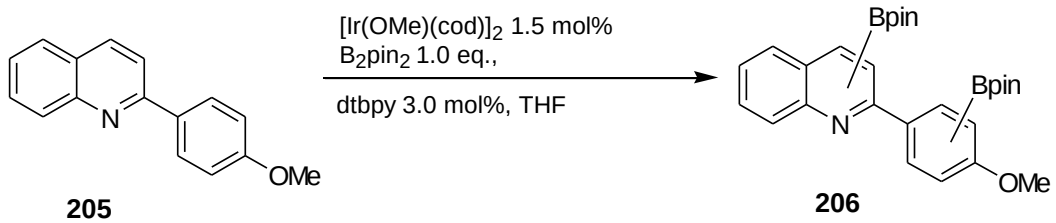
[a]Rt and mass determined by GC-MS

Table 20: Preparation of 2-aryl-quinoline derivatives

These products **199** and **205** were confirmed by GC-MS analysis (**Table 20**). Furthermore, the ^1H NMR spectrum contained a singlet at δ = 2.5 and 3.3 for the two CH_3 and OCH_3, respectively. For these compounds, substitution at C-2 was confirmed by a NOESY correlation between 2'-H and 3-H.

2.1.3 The borylation of 2-(4-methoxyphenyl)-quinoline

With the 2-arylquinolines available attention turned to their borylation. Surprisingly following the conditions described above (**Section 2.1.1.1**) led only to limited conversion of **205** (27% conversion after 120 min). Since this reaction gave low conversion of starting material to borylated compounds, the temperature and time of subsequent reactions was varied (**Table 21**). Ultimately heating the reaction at 100 ^{o}C for 4 h afford ≥ 95% conversion (**entry 3**). More detailed analysis of the crude reaction mixture by GC-MS using the M^+ peaks at Rt = 28.3-29.2 min with *m/z* = 361 ($[MH]^+$); and Rt = 37.5 and 43.0 min with *m/z* = 487 ($[MH]^+$) suggested that this contained 3 mono-and 2 bis-borylated products **206**.



205 **206**

entry No	T ^{o}C	Time h	conv[a] %	ratio (mono):(bis)[a]
1	60	2	27	(9:7:11):----
2	80	15	90	(12:17:17):(19:25)
3	100	4	95	(17:17:15):(18:28)

[a]conversion and ratio determined by GC-MS

Table 21: Borylation of 2-(4-methoxyphenyl)-quinoline

Unfortunately it was not possible to separate these products by silica gel chromatography. Additionally determination of these isomers was difficult by NMR spectrum analysis. In conclusion, whilst good conversion could be achieved through

raising the reaction temperature from 60 °C to 100 °C this also led to the formation of additional bis-borylated products. Whilst the introduction of further substituents e.g 2-aryl-7-methoxyquinoline would provide greater steric control over the second borylation at the 6- and 8-positions of quinoline it was deemed more efficient to explore alternative routes towards the desired quinolones **193**.

2.1.4 Preparation of 2-(aryl)-4-chloro-5-methoxy and 5,7-di-methoxyquinoline derivatives

Through retrosynthetic analysis of the desired product **193**, it was proposed that these products could be prepared through the selective Suzuki cross-coupling of 2-chloro 4-alkoxyquinoline **207** at the 2-position with an arylboronic acid. In turn 2,4-di-chloroquinoline can be obtained from the reaction of quinoline-2,4-dione with $POCl_3$ (**Figure 19**).

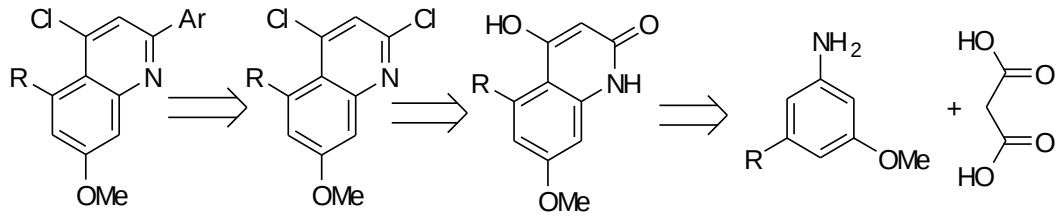
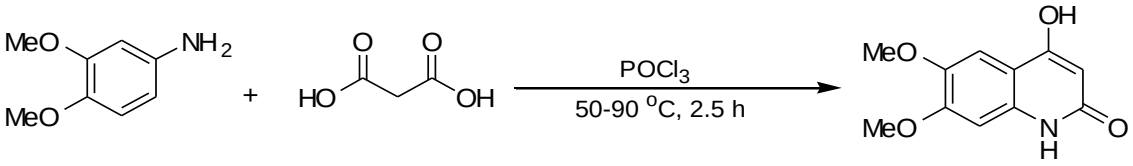


Figure 19: Retrosynthetic analysis of the desired quinoline

2.1.4.1 Quinoline 2, 4-dione derivatives

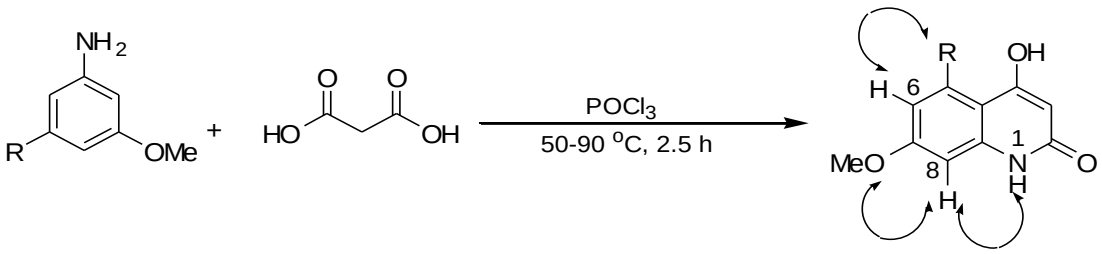
A review of the literature revealed that quinoline-2,4-dione **216** has been prepared by the reaction of 3,4-di-methoxyaniline **215** with malonic acid **208** in the presence of $POCl_3$ (**Scheme 40**).[85]



215 **208** **216 (79%)**

Scheme 40: Preparation of quinoline 2, 4-dione derivatives[85]

Following this precedent, quinoline-2,4-dione **211** was prepared by heating malonic acid **208** with aniline **209** to afford, following trituration with ethanol, the desired quinolone **211** in 43% yield (**Scheme 41**).



209 (R= H)
210 (R= OMe)

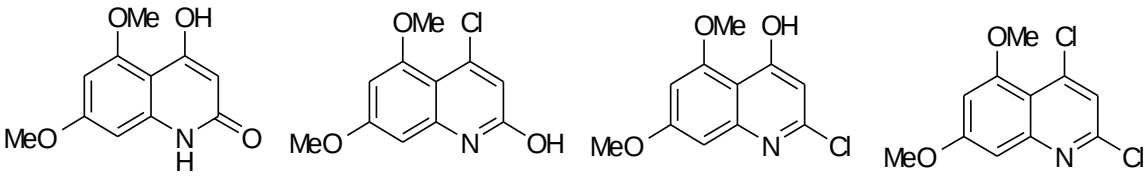
208

211 (R= H, 43%)
212 (R= OCH_3, 49%)

Scheme 41: Preparation of quinoline 2, 4-dione derivatives

Confirmation of this product was obtained from analysis of the ^1H NMR spectrum which contained two broad peaks with high chemical shifts δ = 11.1 and 11.0 corresponding to the OH and NH signals, coupled with a characteristic methoxy signal at δ = 3.8. Further evidence for the quinolone tautomer was provide by a C=O stretch in the IR spectrum at 1626 cm^{-1}. In a similar fashion di-methoxy analogue **212** could be prepared in 49% yield. The relatively low yield of these reactions may be due to the low solubility of the reactants in the reaction medium $POCl_3$. Increasing the volume of $POCl_3$ used led to the production of a mixture of mono chloroquinoline (**217, 218**), di-

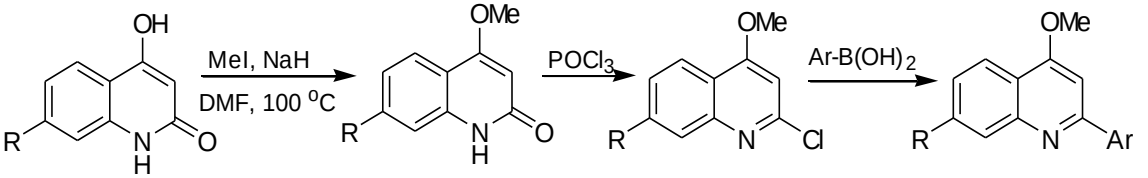
chloroquinoline **214** and quinoline 2,4-dione **212** as observed by LC-MS analysis (**Figure 20**).



212 **217** **218** **214**

Figure 20: **Mixtures of mono-chloro and di-chloroquinoline and quinoline-2,4-dione**

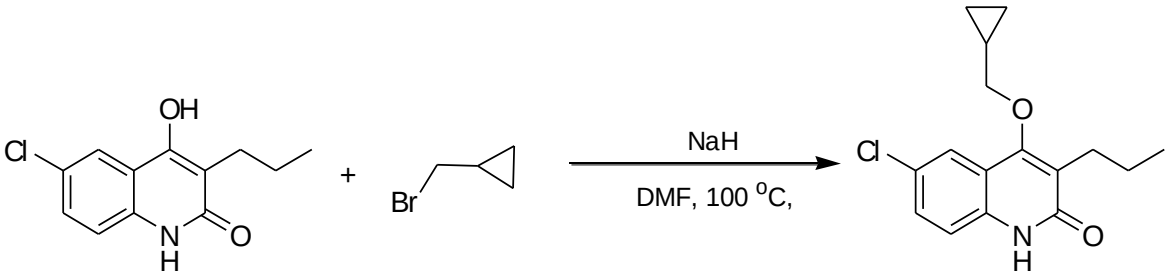
With products **211** and **212** in hand, the next step was the methylation of the OH group to form 4,7-di-methoxyquinoline-2-one **219** and subsequent chlorination **207** to enable a selective Suzuki-Miyaura cross coupling at C-2 **220** (**Scheme 42**).



211 (R = OMe) **219** **207** **220**

Scheme 42: Methylation of quinoline 2,4-dione

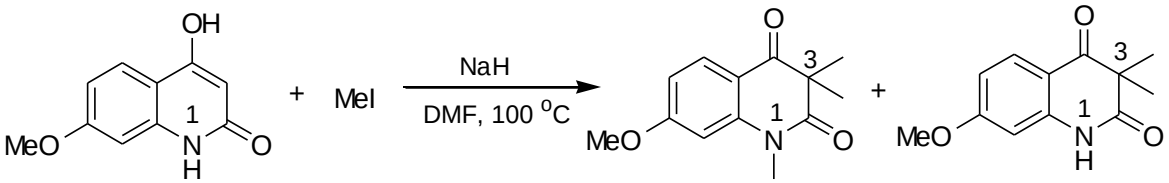
A review of the literature[86] revealed that the reaction of 6-chloro-4-hydroxy-3-propyl-2 (1H)-quinoline **221** and bromomethylcyclopropane **222** resulted in selective o-alkylation **223** (**Scheme 43**).



221 **222** **223** (30%)

Scheme 43: The alkylation of quinoline-2,4-dione[86]

Following this precedent, the substrate **211** and methyl iodide **224** were heated in DMF at 100 °C for 2 h (**Scheme 44**).



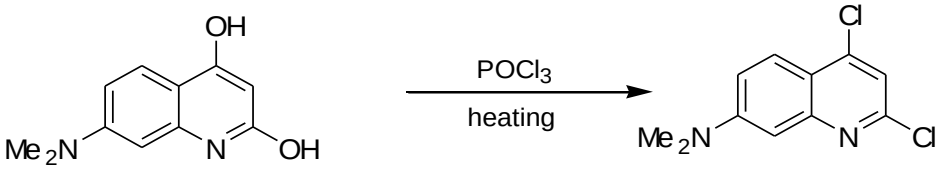
211 **224** **225** (7%) **226** (35%)

Scheme 44: Methylation of quinoline 2,4-dione

However, following chromatography, two isomeric quinolones **225** and **226** were isolated in a yield of 7% and 35%, respectively. Confirmation of these products were obtained by GC-MS, which showed peaks with Rt = 19.9 and 20.5 at *m/z* = 233 ($[M]^+$) and *m/z* = 219 ($[M]^+$) for products **225** and **226** respectively. In addition, further evidence to support the proposed structure was obtained from the ^{1}H NMR spectrum. Both compounds **225** and **226** show characteristic signals at δ = 1.5 for the methyl groups at C-3 whilst the lack of the characteristic OH, and 3-H signals at δ= 11.1 and 5.6 was consistent with a loss of the keto-enol functional group. With this disappointing result, synthesise of 2,4-di-chloroquinoline **213** was carried out to test the extent to which a regioselective Suzuki-Miyaura cross coupling could be achieved.

2.1.4.2 2, 4-Di-chloroquinoline derivatives

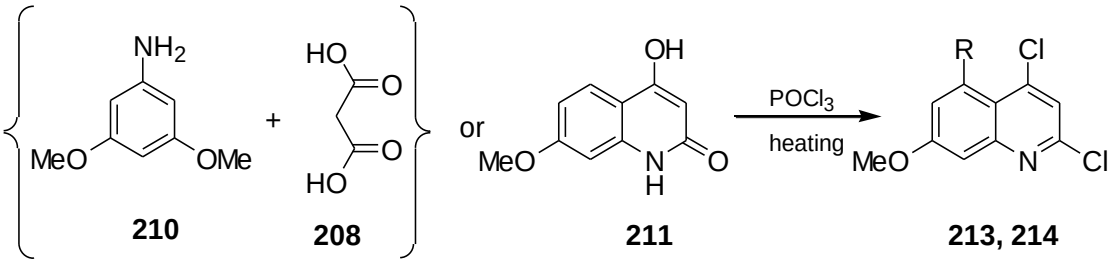
A survey of recent methods[87] revealed that di-chloroquinoline **228** could be prepared by heating 2,4-dihydroxy-7-(di-methylamino)quinolone **227** with $POCl_3$ (**Scheme 45**). Since these hydroxyquinolones were the initial product formed in the reactions discussed above it was speculated that longer reaction times with excess of $POCl_3$ would provide the desired di-chloroquinoline.



227 **228**

Scheme 45: Preparation of di-chloroquinoline

Consistent with this idea, heating quinolone **211** in $POCl_3$ following quenching and neutralizing of the crude mixture, afforded the desired quinoline **213** in a very good yield of 95% (**Table 22**). Confirmation of this product was obtained by GC-MS analysis which showed the correct isotopic ratio 1:6:9 of di-chlorine. Furthermore, the ^1H NMR spectrum showed a characteristic 3-H signal in the de-shielded region at δ = 7.4 and lacked the characteristic OH and NH signals at δ = 11.1 and 11.0, respectively. In a similar fashion the di-methoxy analogue **214** was prepared in 71% yield.



Comp No	R	T ^{o}C	R. time h	Yield%
213	H	105	1	95
214	OMe	50-105	2	71[a]

a: A yield over two steps

Table 22: Preparation of di-chloroquinoline derivatives

With these products in hand, synthesis of 2-arylquinoline was undertaken. Initially a S_NAr strategy was explored. As such, 4-methoxy phenyl lithium **229** was prepared by the addition of nBuLi to arylbromide **1** at -78 ^{o}C (**Figure 21, EQ 1**). This reaction mixture was then added to the substrate **213** in THF at -78 ^{o}C for 1 h (**Figure 21, EQ 2**). Unfortunately, the reaction returned unreacted starting material along with undesirable products **231** and **232** as indicated by GC-MS analysis (**Scheme 46**).

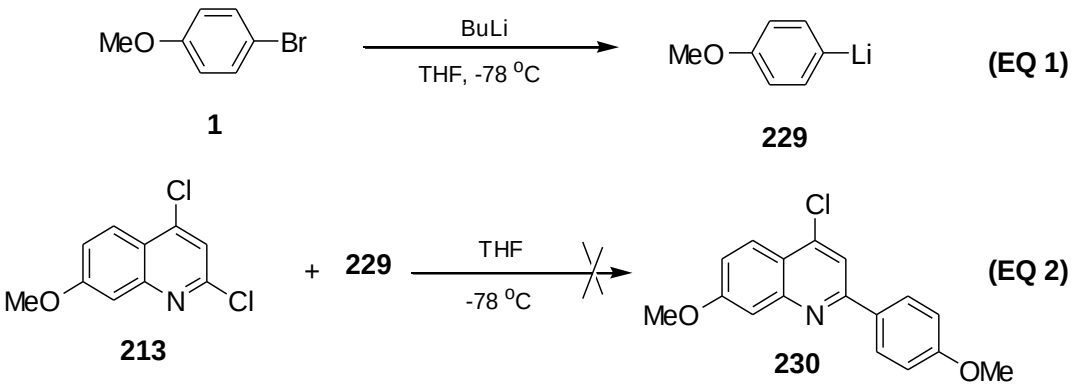
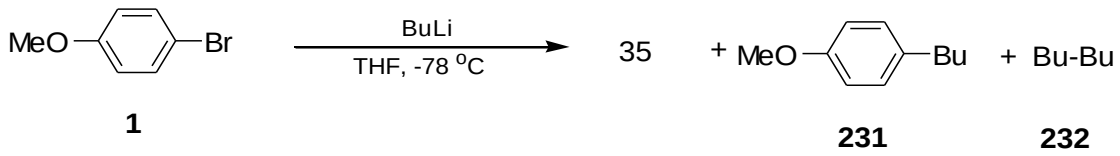


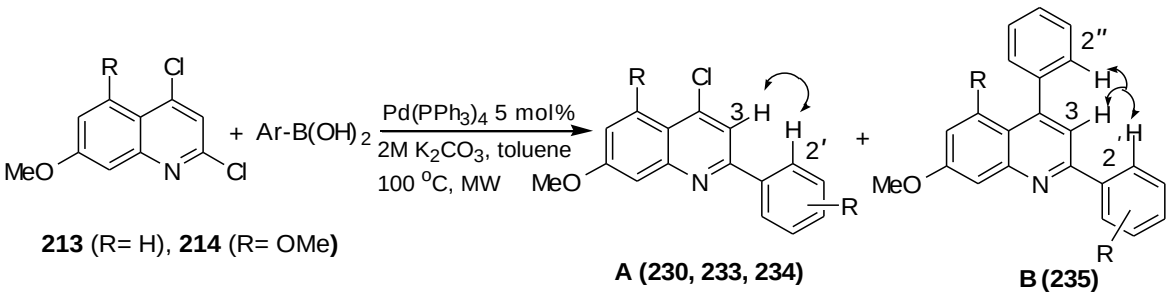
Figure 21: EQ 1 & EQ 2: Preparation of 2-(aryl-substitution)-quinoline using alkyl lithium



1 **231** **232**

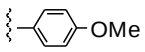
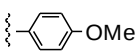
Scheme 46: The undesirable products 231 and 232 through adding BuLi

Consequently an alternative pathway based on Suzuki-Miyaura cross coupling was investigated. Following the procedure developed (**Section 2.1.2**, **Table 20**), reaction of di-chloroquinoline **213** and **214** with arylboronic acid **5** and **198** at 100 °C in the presence of $Pd(PPh_3)_4$ afforded the desired aryl quinolines **230**, **233** and **234** in 32-75% yields (**Table 23**).



213 (R= H), **214** (R= OMe**)**

A (230, 233, 234) **B (235)**

entryNo	Ar	time h	Ar-B(OH)$_2$ eq.	R	Pro. No A:B	conv[a] %	ratio (A:B)[a]	A : B yield%
1		2.5	1.5	H	**230**:---	100	(89:11)	75:----
2		1/2	1.0	H	**233**:---	100	(99:01)	60:-----
3		1	1.15	OMe	**234**:**235**	100	(83:17)	32:9

[a]Conversion was determined by GC-MS

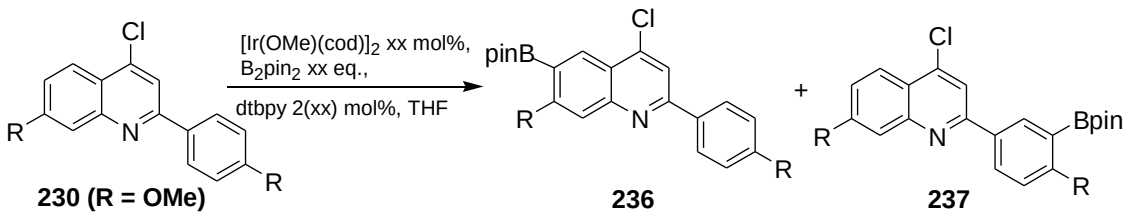
Table 23: Preparation of 2-(4-methoxy and 3,5-di-methylphenyl)-quinoline derivatives

Confirmations of these products were obtained by GC-MS, which indicated that the isotopic ratio of the fragmentations changed from 1:6:9 to 1:3 indicating loss of a

chlorine atom. For both analogues substitution at C-2 was confirmed by a NOESY correlation between 2'-H and 3-H. whilst for product **235** confirmations of substitution at C-4 was revealed by correlations between 2"-H and 3-H (**Table 23**).

2.1.5 The borylation of 2-(4-methoxyphenyl)-4-chloro-7-methoxyquinoline

With compounds **230** and **233** available, the next task was to study the borylation reaction with the hope that the combination of substituents at the 4'-, 4- and 7-positions would direct borylation to C-5. However this proved not to be the case and afforded a complex mixture of mono-borylated products with unreacted starting material (**Table 24**). More detailed analysis by GC-MS integrating the M^+ peaks at Rt = 32.9 and 32.3 min both with *m/z* = 425 ([M (^{35}Cl)]$^+$, indicated that the crude mixture contained 2 mono-borylated products **236** and **237**. Such borylation *ortho* to a methoxy group is not unprecedented. It has been observed through the borylation of 4,4'-di-methoxy-2,2'-bipyridine.[88]



230 (R = OMe) **236** **237**

entry No	Ir mol%	B_2pin_2 (eq.)	T ^oC	Time (h)	conv[a] (%)	ratio (236):(237)[a]	ratio (236):(237)[b]
1	1.5	1.0	100	1	60	(6.5:1.0)	----------
2	2.5	2	100	1	73	(5.4:1.0)	5.9:1.0:----
3	5.0	2	100	2	74	(7.2:1.0)	----------

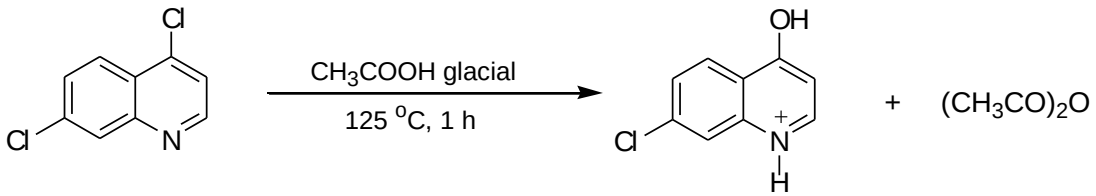
[a]conversion and ratio determined by GC-MS; [b]ratio determined by ^{1}H NMR

Table 24: Borylation of 2-(4-methoxyphenyl)-4-chloro-7-methoxyquinoline

In order to enhance the percentage conversion, the loading of both catalyst and diboron reagent were increased (entry **2** and **3**). Whilst modest enhancements in the selectivity could be obtained it was not possible to achieve a completely selective reaction under these conditions. However, even with increased catalyst loading and temperature the borylation of 2,4-di-chloro-7-methoxyquinoline **213** showed no conversion by GC-MS. The regiochemistry for each adduct **236** and **237** was ascertained by analysis of the ^{1}H NMR spectrum which showed five characteristic proton signals for product **236** and seven characteristic proton signals for product **237**. Significantly the alpha boryl hydrogen at 5-H and 2'-H showed a distinctive shift to higher frequencies, δ = 8.5 and 8.4 for **236** and **237**, respectively.

2.1.6 Preparation of *N*-methyl-2-(4-methoxyphenyl)-7-methoxyquinoline-4-one

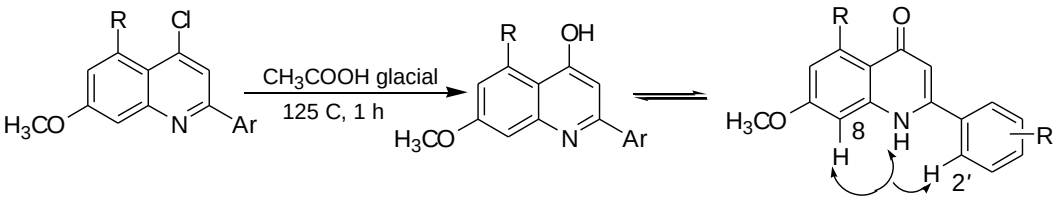
Since the borylation reaction was not giving the desired regiochemistry; in order to complete the synthesis of quinolone **238,** the selective hydrolysis of the 4-chloroquinoline **230** was explored.



141 **239 (88.5%)**

Scheme 47: Preparation of 7-chloro-4-hydroxyquinoline hydrochloride

Based on literature precedent[89] for this transformation **239** (**Scheme 47**), 4-chloro-quinoline derivatives **230** were heated with glacial acetic acid at 125 °C for 1 h and then the mixture adjusted with 3M NaOH to pH = 8-9 (**entry 1**, **Table 25**).



230, 233, 234 **241A** **192B, 240B**

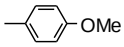
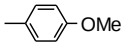
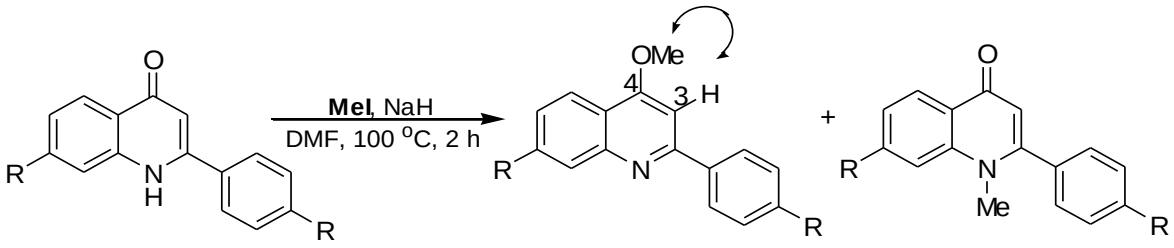
entry No	Ar	R	prod.No	Yield%
1		H	**192B**	45
2		H	**240B**	37
3		OMe	**241A**	45

Table 25: Preparation of 2-aryl-7-methoxy and 5,7-di-methoxyquinoline-4-one derivatives

Following trituration of the crude mixture, the desired product **192B** was isolated in yield of 45%. Confirmation of this product was obtained by LC-MS which indicated a lack of the isotopic ratio for a chlorine atom. Additionally, the ^{1}H NMR spectrum indicated a characteristic NH signal at δ = 11.4 showing a NOESY correlations between (2'-H and 8-H with NH). Further evidence for the quinolone tautomer was provide by a C=O stretch in the IR spectrum at 1626 cm^{-1}. In a similar fashion quinolones analogue **240B** and **241A** could be prepared in 37% and 45% yields respectively (**Table 25**). Having successfully established a route to the desired quinolone the final objective was to develop methodology for *N*-alkyltion of **192B**. As discussed in **section 2.1.4.1,** similar compounds have been previously prepared. Following similar protocols **192B** and MeI **224** were heated at 100 °C for 2 h (**Scheme 48**). In the crude mixture, GC-MS analysis

showed two peaks at Rt = 27.2 and 30.9 min both with molecular ion at *m/z* = 295 ($[M]^+$) with a 1:1 ratio of **242**:**238**, indicating that the crude mixture contained 2 mono methylated products presumably **242** and **238**.



192B (R = OMe) **242 (20%)** **238**

Scheme 48: Methylation of OH group

However, following chromatography, only the undesired quinoline **242** could be isolated in a yield of 20%. The hypothetical N-methylated product **238** could not be detected. Confirmation of product **242** was obtained by GC-MS analysis. Additionally, the ^{1}H NMR spectrum showed the characteristic methyl signal of the methoxy group at 4-position at δ = 3.9, and lacked the characteristic NH signal at δ = 11.4 that appeared in compound **192B.** Finally this compound substitution at C-4 was confirmed by a NOESY correlation between 4-OCH_3 and 3-H (**Scheme 48**).

2.17 Summary and Conclusions

In this work 2-aryl quinoline derivatives were prepared using two strategies Baran's and Suzuki-Miyaura coupling protocols. Borylation of 2-(4'-methoxyphenyl)-quinoline **205** gave a complex mixture of mono- and bis-borylated products. In order to minimise the number of different borylated products, highly substituted 2-arylquinoline derivatives were successfully prepared starting from 3-methoxy and 3,5-dimethoxy aniline derivatives and malonic acid. The resulting 2,4-dichloro-quinoline derivatives

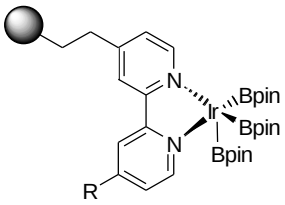
were then coupled with aryl halides in a Suzuki-Miyaura reaction. The borylation of highly substituted quinoline **230** unexpectedly afforded the two mono-borylated products at the 6- and 3'-position. This result was consistent with the borylation of 4,4'-di-methoxy-2,2'-bipyridine **69**. Methylation of quinolone **192B** did not afford the desired N-alkylation product **238**. Disappointingly, 2,4-dichloro-7-methoxy quinolone **213** proved to be resistant to Ir(dtbpy)$(Bpin)_3$ **88A** catalyst borylation **(Section 1.1.5, Figure 8)**.

Chapter 3

3 Preparation and evaluation of 4,4'-di-substituted-2,2'-bipyridine derivatives

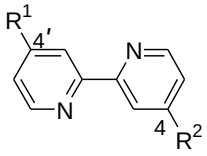
3.1 Introduction

A major goal of the project was to synthesise a polymer supported iridium catalyst for the borylation of aromatic and heteroaromatic compounds, which could be recovered using simple filtration and then re-used for further reactions (**Figure 22**). As dtbpy **22** is a common ligand choice for borylation reactions, the aim of this work was to prepare model bipyridine derivatives bearing electron-donating groups at the 4- and 4'-position, which are suitable for coupling to a polymer support (**Figure 23**). In addition to enhancing reactivity it was interesting to also test the selectivity of each new ligand in the borylation of non-symmetrical substrates and compare it to that obtained with dtbpy **22**.



R= electron-donating

Figure 22: Polymer supported iridium catalyst

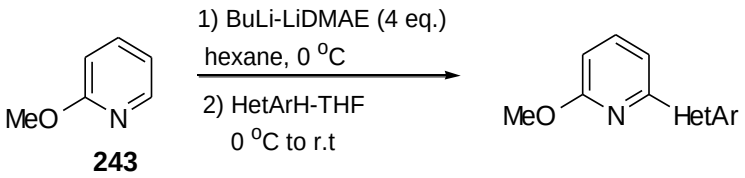


R^1, R^2 = electron-donating groups

Figure 23: 4,4'-di-substituted-2,2'-bipyridine derivatives

3.1.1 Preparation of 4,4'-di-substituted-2,2'-bipyridine derivatives

As discussed above an efficient route to unsymmetrical bipyridine derivatives was needed. Initial studies focused on the simple addition of a α-pyridyl organometallic to a C-2 substituted pyridine. Precedents for this approach can be found in a report by Gros *et al.*[90] (**Table 26**). In this work, the reaction of 2-methoxypyridine **243** with BuLi-LiDMAE afforded the lithiated pyridine, which could then be combined with a range of heteroaromatic compounds to afford new bipyridine derivatives **244-246** in reasonable yields.



243

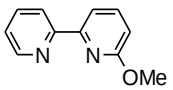
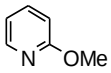
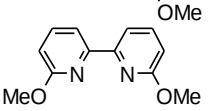
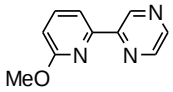
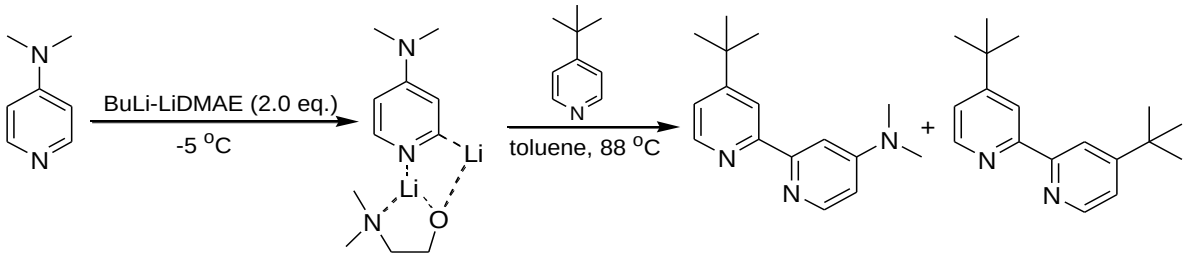
Comp No	HetAr	Products	Yield %
244			**64**
245			**60**
246			**58**

Table 26: Coupling of pyridine with heteroaromatic compounds[90]

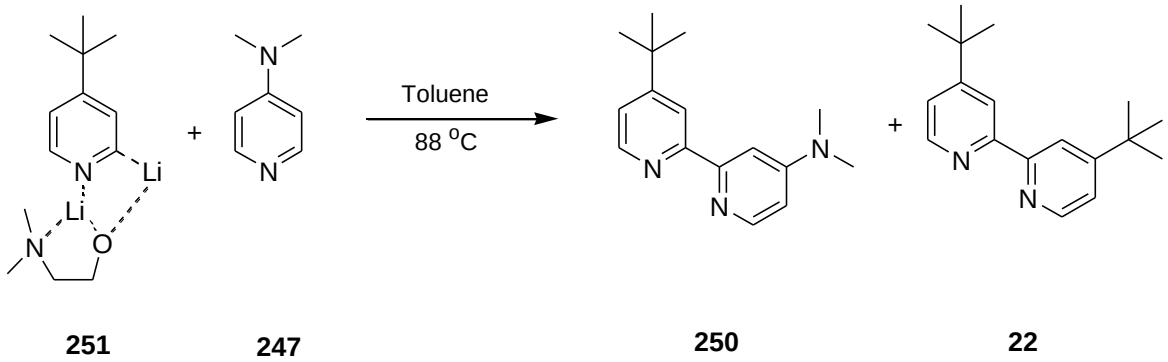
Following this example, DMAP **247** was metallated, using n-BuLi-LiDMAE (2.0 eq) at -5 °C to give the lithiated pyridine complex **248** as a red solution. Then 4-tert-butylpyridine **249** (1.2 eq) in toluene was added and the mixture heated at 88 °C for 22 h (**Scheme 49**). GC-MS analysis of the reaction mixture revealed that the formation of

two products, corresponding to the desired product **250** (*m/z* = 255) and dtbpy **22** (*m/z* = 268).



Scheme 49: Addition of 2-lithiated-DMAP 248 to 4-tert-butylpyridine 249

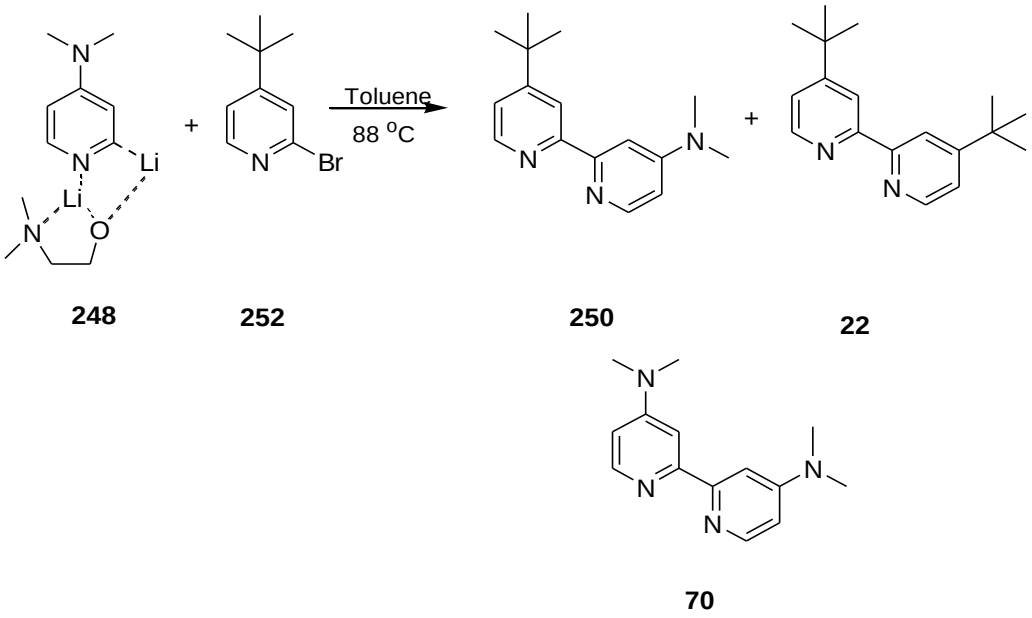
The formation of dtbpy **22** suggested that the proton transfer between the pyridines is faster than nucleophilic attack**.** Attempts to increase the selectivity to form the bipyridine **250**, by either slow addition of the anion **248** to tert-butylpyridine **249,** or by forming the anion of tert-butylpyridine **251** first and adding DMAP **247,** were not successful **(Scheme 50)**.



Scheme 50: Addition of 2-lithiated-4-tert-butylpyridine 251 to DMAP 247

With the idea that introducing a better leaving group would enhance the substitution reaction, the use of 2-bromopyridine **252 (the synthesis of which is discussed in section 3.1.3.1)** as the electrophile was explored. Disappointingly initial experiments

using lithiated DMAP **248** as the nucleophile were not successful giving only low conversion as determined by GC-MS analysis (**Scheme 51**).

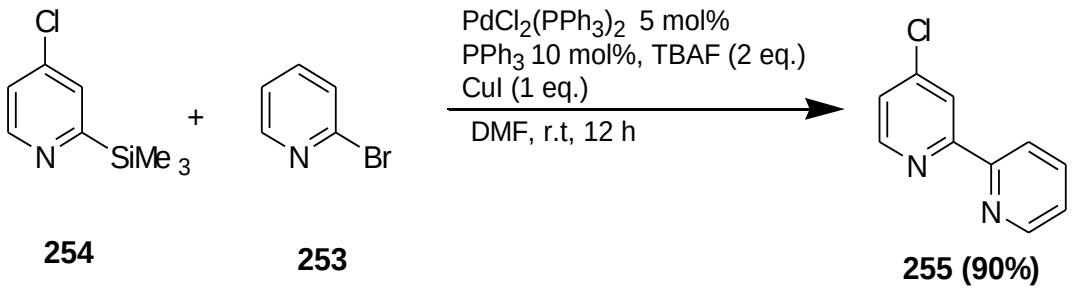


Scheme 51: Addition of 2-lithiated-DMAP 248 to 2-bromo-4-tert-butylpyridine 252

Given these selectivities as well as the difficulties in separating the desired product by chromatography it was decided to explore alternative routes to bipyridines using transition metal coupling reaction.[91] The first coupling reaction to be investigated was the Hiyama cross-coupling reaction. This will be discussed in the next section.

3.1.2 Preparation of 4,4'-substituted-2,2'-bipyridine derivatives via the Hiyama cross-coupling reaction

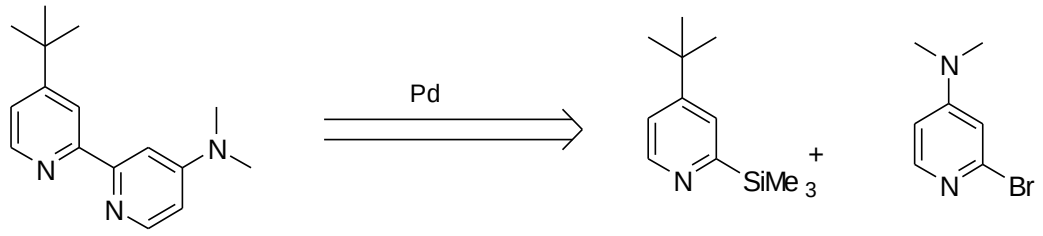
A literature search revealed that similar compounds have been prepared by coupling of 2-bromopyridine **253** and 4-chloro-2-tri-methylsilylpyridine **254** using $PdCl_2(PPh_3)_2$ as the catalyst in presence of TBAF and CuI as an activating agent to afford the desired bipyridine product **255** in 90% yield (**Scheme 52**).[92]



254 **253** **255 (90%)**

Scheme 52: Hiyama cross-coupling reactions[92]

Following this precedent for the synthesis of 4'-(di-methylamino)-4-tert-butyl-2,2'-bipyridine **250**, 2-(tri-methylsilyl)-4-tert-butylpyridine **256** and 2-bromo-4-di-methylaminopyridine **257** were required (**Figure 24**).

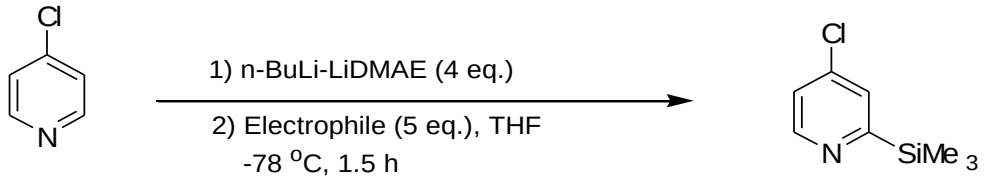


250 **256** **257**

Figure 24: Retrosynthetic analysis of 4'-di-methylamino-4-tert-butyl-2,2'-bipyridine 250

3.1.2.1 Preparation of 2-(tri-methylsilyl)-4-substituted pyridine

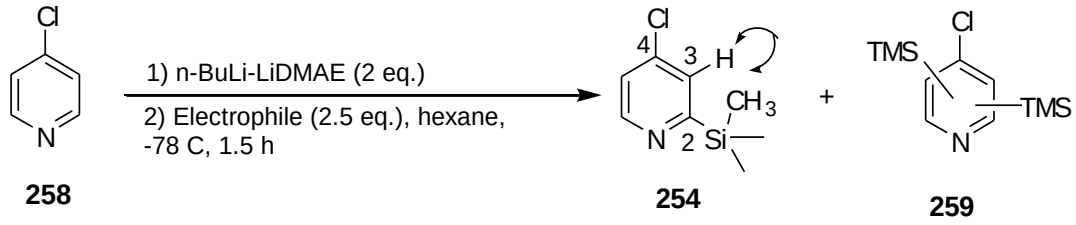
Fort *et al*.[93] have shown that similar compounds have been prepared through lithiation of 4-chloropyridine **258** using BuLi-LiDMAE (**Scheme 53**).



258 **254 (85%)**

Scheme 53: Preparation of 4-chloro-2-tri-methylsilyl pyridine 254[93]

Following this precedent, a 99% conversion of 4-chloropyridine **258** with a ratio of 91:8 (**254:259**) was obtained (**Scheme 54**). Analysis of the crude reaction mixture by LC-MS revealed the presence of a mixture of mono and di-substituted pyridine, with peaks at Rt = 2.4 and 3.7 min with *m/z* = 188 ([MH (^{28}Si, ^{37}Cl)]$^+$ and 258 ([MH (^{28}Si, ^{28}Si, ^{35}Cl)]$^+$) respectively. Following purification by chromatography, the desired silyl product **254** was obtained in 44% yield.



258 **254** **259**

LC-MS Conv (%)	ratio (254 : 259)	(254) Yield%
99	91 : 8.0	44

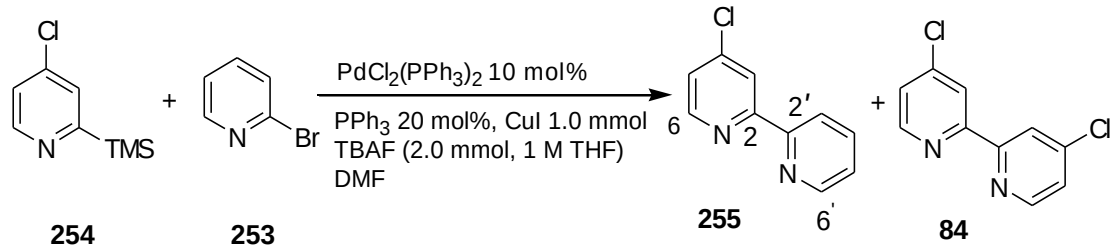
Scheme 54: Preparation of 4-chloro-2-tri-methylsilylpyridine 254

Confirmation of the proposed structure was obtained from a NOESY spectrum, which showed a correlation between the $SiCH_3$ (δ=0.6 ppm) and the 3-H signal (δ=7.82).

3.1.2.2 Preparation of 4-chloro-2,2'-bipyridine[92]

With silyl pyridine **254** in hand, cross coupling with 2-bromopyridine **253** was explored (**Scheme 55**). LC-MS analysis of the reaction mixture revealed that complete conversion of starting material had occurred, which resulted in the formation of two products with a ratio of 84:16, the desired product **255** at Rt = 3.0 with *m/z* = 193 ([MH (^{37}Cl)]$^+$, 35%), 191 ([MH (^{35}Cl)]$^+$, 35%) and the homo coupling product **84** at Rt =3.8 with

m/z = 229 ([MH (^{37}Cl,^{37}Cl)]$^+$, 11%), 227 ([MH (^{35}Cl,^{37}Cl)]$^+$, 55%), 222 ([MH (^{35}Cl,^{35}Cl)]$^+$, 100%) (**Scheme 55**).

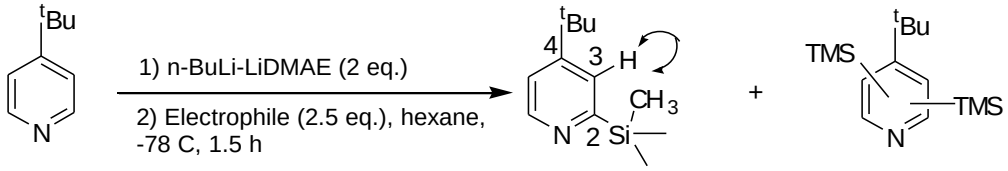


254 **253** **255** **84**

LC-MS conv (%)	ratio (255 : 84)	(255) Yield%
100	84 : 16	54%

Scheme 55: Preparation of 4-chloro-2,2'-bipyridine 255

Following chromatography the desired 4-chloro-2,2'-bipyridine **255** was isolated in 54% yield. The structure was confirmed by the presence of characteristic 6'-and 6-signals in the ^{1}H NMR spectrum [δ = 8.7 (1H, d, *J* = 4.8 Hz) and 8.6 (1H, d, *J* = 5.3 Hz), respectively]. With the viability of a Hiyama cross-coupling strategy established, attention then turned to the bipyridine **250**. In order to prepare the desired bipyridine **250**, 4-tert-butyl-2-tri-methylsilylpyridine **260** was needed. As before, lithiation of 4-tert-butyl pyridine **249** followed by reaction with TMSCl afforded the desired silylated pyridine **260** albeit in only 17% yield (**Scheme 56**).



249 **260** **261**

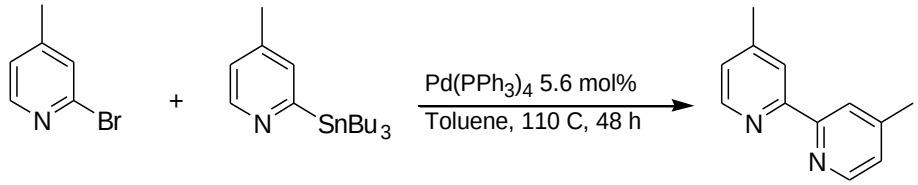
LC-MS Conv (%)	ratio (260 : 261)	(260) Yield%
48	48 : 0	17

Scheme 56: Preparation of 4-tert-butyl-2-tri-methylsilylpyridine 260

A possible reason for the low yield of the desired silyl product **260** might be due to a need for an electron withdrawing group.[92-95]Despite considerable experimentation no significant improvement in yield could be obtained. Consequently attention turned to the use of the Stille cross-coupling reaction, described in the next section.

3.1.3 Preparation of 4,4'-substituted-2,2'-bipyridine derivatives via the Stille cross-coupling reaction

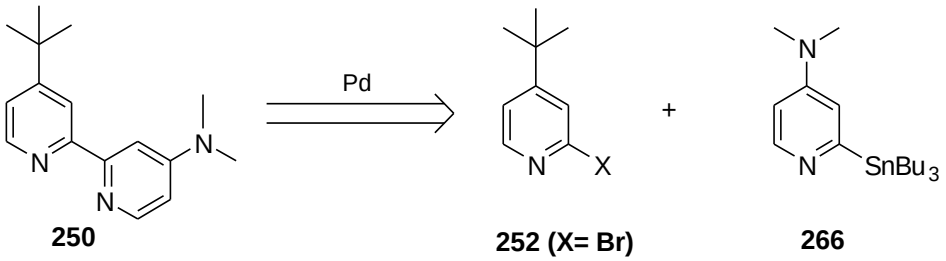
A survey of the literature revealed that similar compounds have been prepared through the Stille cross-coupling reaction. For example Schubert *et al.*[96] have described the reaction of 2-bromo-4-methylpyridine **262** with 2-tri-butylstannyl-4-methylpyridine **263** using $Pd(PPh_3)_4$ as the catalyst to afford bipyridine **264** in 67% isolated yield (**Scheme 57**).



262 **263** **264 (67%)**

Scheme 57: Preparation of 4,4'-di-methyl-2,2'-bipyridine 265[96]

In order to exploit this precedent for the synthesis of 4'-(di-methylamino)-4-tert-butyl-2,2'-bipyridine **250**, 2-bromo- or 2-chloro-4-tert-butylpyridine (**252** and **265** respectively) and 4-(di-methylamino)-2-(tri-butylstannyl)-pyridine **266** were required (**Figure 25**).

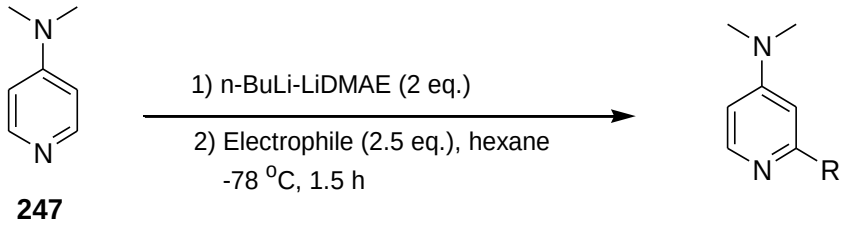


250 **252 (X= Br)** **265 (X= Cl)** **266**

Figure 25: Retrosynthetic analysis of 4'-di-methylamino-4-tert-butyl-2,2'-bipyridine 250

3.1.3.1 Preparation of 2-bromo and tri-butylstannyl-4-substituted pyridine

Fort *et al.*[97] have shown that a range of 2-functionalised pyridines **266-269** can be generated through trapping of a 2-lithiated pyridine **247** with diverse electrophiles (**Table 27**).

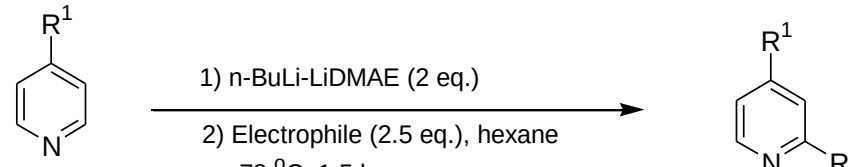


247

Electrophile	Prod No	R	Yield%
$ClSnBu_3$	**266**	$SnBu_3$	70
CBr_4	**267**	Br	94
I_2	**268**	I	81
C_2Cl_6	**269**	Cl	90

Table 27: Preparation of 2-substituted DMAP[97]

Following this precedent, lithiation of DMAP **247** with n-BuLi-LiDMAE, followed by addition of tri-butyltin chloride, afforded, following purification by chromatography, the desired stannyl product **266** in 61% yield (**Table 28**).

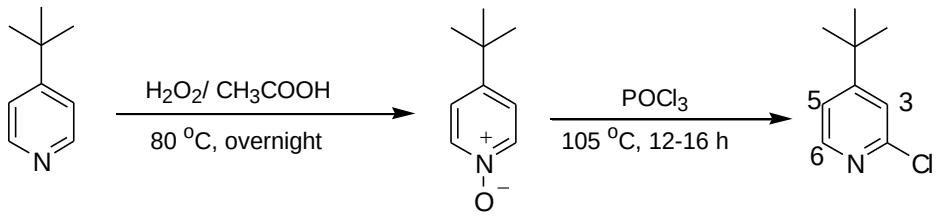


247 (R^1= NMe_2)
249 (R^1= ^tBu)

Prod No	Electrophile	R^1	R	Yield%
266	$ClSnBu_3$	$N(CH_3)_2$	$SnBu_3$	61
267	CBr_4	$N(CH_3)_2$	Br	45
252	CBr_4	$(CH_3)_3$	Br	52

Table 28: Preparation of 2-substituted DMAP and terbutylpyridine

Confirmation of **266** was obtained from LC-MS analysis, which showed a peak at Rt = 2.55 min with the expected Sn isotope pattern [*m/z* = 416 ($[M]^+$, Sn^{124}), 414 ($[M]^+$, Sn^{122}), 410 ($[M]^+$, Sn^{120})]. Further confirmation of the proposed structure was obtained from the ^1H NMR spectrum which showed characteristic butyl signals at δ = 0.86, 1.32, 1.55 and 1.1 ppm and the correct number of proton signals at δ = 6.6, 6.3 and 8.3 ppm for the protons at the 3-, 5- and 6-positions of the pyridine ring with the expected coupling pattern for a 2,4-di-substituted pyridine. In a similar fashion substituting tri-butyltin chloride for CBr_4 afforded, following chromatography, 2-bromopyridines **267** and **252** in 45 and 52% yield respectively. The proposed structures of these products were confirmed by GC-MS analysis, which showed the bromine isotope pattern. The 2-chloro analogue **265** was prepared by an alternative, simpler protocol involving oxidation to the *N*-oxide [Rt = 2.05 (*m/z* = 151 $[M]^+$)], and subsequent chlorination using $POCl_3$[98] (**Scheme 58**).



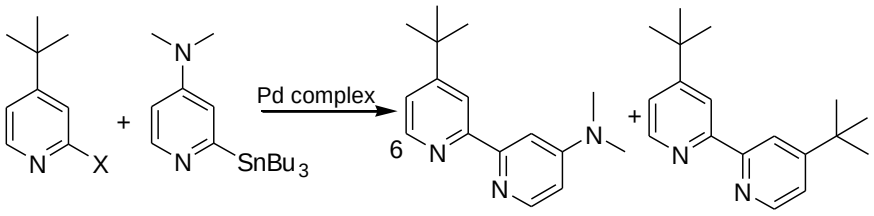
249 **270 (82%)** **265 (79%)**

Scheme 58: Preparation of 2-chloro-4-tert-butylpyridine 265[98]

Confirmation of this product was obtained by GC-MS, which contained a single component with Rt = 6.1 min. The molecular ion showed the expected Cl isotope pattern [*m/z* = 169 ([M (^{35}Cl)]$^+$, 100%) and *m/z* = 171 ([M (^{37}Cl)]$^+$, 32%)].

3.1.3.2 Preparation of 4'-di-methylamino-4-tert-butyl-2,2'-bipyridine

With the key building blocks in hand, attempts to generate the desired bipyridine **250** explored the cross-coupling of 2-bromo and chloro-4-tert-butylpyridine **252** and **265** with 4-di-methylamino-2-tri-butylstannylpyridine **266** using palladium complexes as the catalyst (**Table 29**).[96,97,99]



252 (X= Br)
265 (X= Cl) **266** **250** **22**

entry No	Pd complex	X	solvent	T °C	time (h)	conv (%)	yield% (250)
1	$Pd(PPh_3)_4$ 3.6 mol%	Br	toluene	110	48	84[a]	---
2	$PdCl_2(PPh_3)_2$ 10 mol%	Br	DMF	110	18	100[a]	13
3	$PdCl_2(PPh_3)_2$ 5 mol% PPh_3 10 mol%	Br	xylene	130	24	100[b]	32[*]
4	$PdCl_2(PPh_3)_2$ 10 mol%	Cl	DMF	100	18	100[b]	32

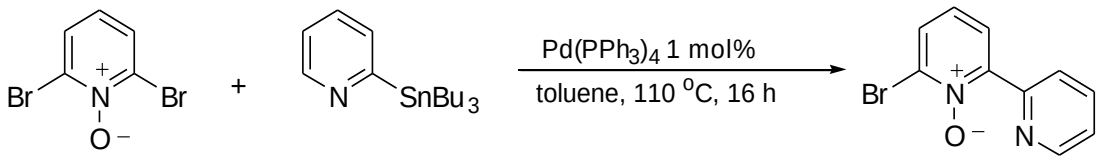
[a]ratio determine by GC-MS, [b]ratio determine by LC-MS, [*](14% yield of 22 could be isolated)

Table 29: Stille cross-coupling reaction using Pd catalysis

The first experiment (**Table 29**, **entry 1**) followed the precedent reported by Schubert[96] (**Scheme 57**), affording a 84% conversion of the starting material **252** as determined by GC-MS analysis. New signals were observed at Rt = 12.4 min with *m/z* = 255 ($[M]^+$) and Rt = 10.9 min with *m/z* = 268 ($[M]^+$) consistent with the formation of **250** and **22**.

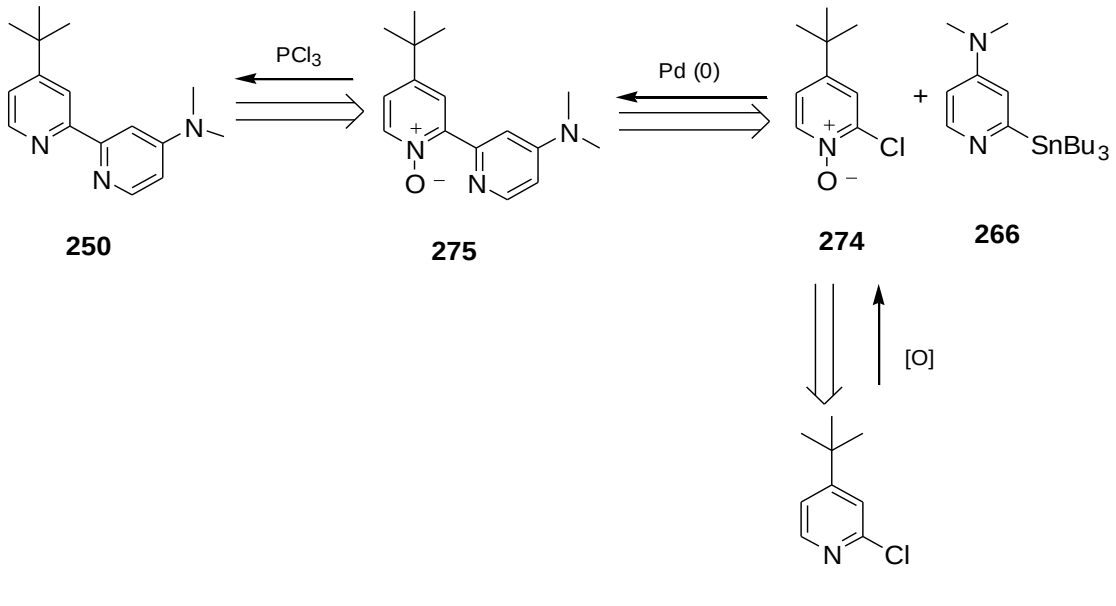
Attempts were then made to form the only bipyridine **250** by varying the conditions and catalyst (**Table 29, entries 2-4**). Replacing $Pd(PPh_3)_4$ with $PdCl_2(PPh_3)_2$ as reported by Verniest[99] gave completely conversion of starting material **252** and **265**, but led to a mixture of **250** and **22** (**Table 29**, **entries 2 & 4**). Ultimately the best conditions for the Stille cross-coupling reaction were found to be $PdCl_2(PPh_3)_2$ with PPh_3[97] (**Table 29**, **entry 3**). Purification of product **250** from the tin residues could be achieved by extraction with 6 M HCl. However, this led to considerable loss of yield. Consequently, although more challenging, direct chromatography of the crude reaction mixture on silica gel, eluting with 5:1:5 Et_3N:EtOAc:hexane afforded **250** in 32% isolated yield accompanied by **22** in 14% yield **(Table 29, entry 3)**. Confirmation of these products was obtained by LC-MS or GC-MS analysis, which showed the correct mass spectra for products **250** and **22**. Additionally, confirmation of the proposed structure was obtained from the ^{1}H NMR spectrum. Compound **250** shows characteristic methyl signals at δ = 1.38 and δ = 3.11 for the tert-butyl and *N*,*N*-di-methy groups at 4-position, while compound **22** only shows the characteristic tert-butyl signal at δ = 1.4. Compound **250** showed characteristic ^{1}H NMR signals at δ = 8.6 (1H, d, *J* = 5.2 Hz), and 8.3 (1H, d, *J* = 6.0 Hz) assigned to the 6- and 6’ -hydrogens respectively, while compound **22** only showed characteristic ^{1}H NMR signals at δ = 8.6 (1H, d, *J* = 5.2 Hz) for both 6- and 6′-hydrogens. Both 2-chloro and 2-bromo-4-tert-butylpyridine were used for the cross-coupling reaction with 4-di-methylamino-2-tri-butylstannylpyridine **266 (Table 29, entries 3 and 4)**. Although LC-MS showed 100% conversion of the starting material for both reactions it proved not possible to translate this into good yields of the desired bipyridine product **250**. Attempts to enhance the yield of the desired bipyridine product **250** by increasing the amount of palladium (II) to 10 mol%

at 110 °C in DMF were not successful. This result may be due to coordination of the palladium catalyst by the pyridyl nitrogen. It was subsequently reasoned that use of an *N*-oxide would minimise the homocoupling of **274** owing to electronic repulsion from the mutually *ortho N*-oxides. This suggestion was supported by the observation that similar compounds have been prepared by coupling 2,6-di-bromopyridine-*N*-oxide **271** with 2-tri-butylstannylpyridine **272** using 1 mol% $Pd(PPh_3)_4$ (**Scheme 59**).[100]



271 **272** **273 (66%)**

Scheme 59: Preparation of 6-bromo-2,2'-bipyridine-*N*-oxide 273[100]

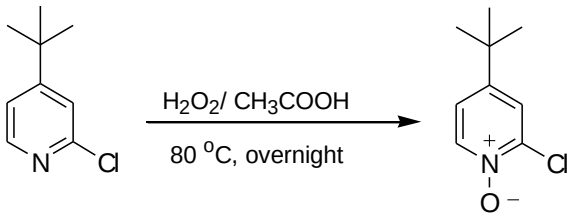


250 **275** **274** **266** **265**

Figure 26: Retrosynthetic analysis of 4'-(di-methylamino)-4-tert-butyl-2,2'-bipyridine 250

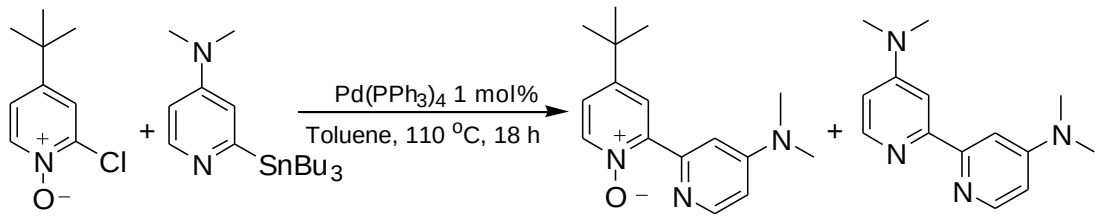
3.1.3.2.1 Preparation of 2-chloro-4-tert-butylpyridine-*N*-oxide

Consequently 2-chloro-4-tert-butylpyridine-*N*-oxide **274** was prepared through reaction of **265** with H_2O_2/ AcOH (**Scheme 60**)[98]. Confirmation of this product was obtained by LC-MS analysis which showed a peak at Rt = 2.3 min with *m/z* = 185 ([M (^{35}Cl)]$^+$). With **274** available, the next step was to explore the coupling of **274** with **265** in a Stille cross-coupling reaction. Following the precedents described above, coupling of 2-chloro-4–tert-butylpyridine-*N*-oxide **274** with 4-(di-methylamino)-2-tri-butylstannylpyridine **266** (1.2 eq.), using 1 mol% $Pd(PPh_3)_4$, afforded the desired bipyridine-*N*-oxide **275 (Scheme 61).** Although the bipyridine-*N*-oxide **275** was afforded without any homo coupling of **274,** the reaction did not proceed to completion. It was suggested that this may be due to oxidation of Pd(0) to Pd(II).



265 **274 (83%)**

Scheme 60: Preparation of 2-chloro-4-tert-butylpyridine-*N*-oxide 274[98]



274 **266** **275** **70**

Conv (%) LC-MS	ratio (275 : 70)
41	16 : 25

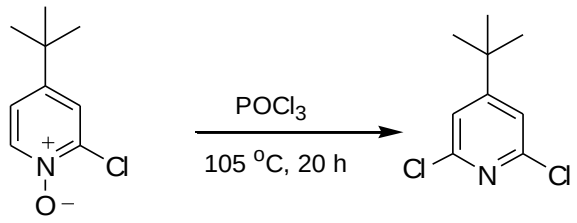
Scheme 61: Preparation of 4'-(di-methylamino)-4-tert-butyl-1-oxy-2,2'-bipyridine 275

Given this disappointing result, an alternative means of control for the coupling reaction was sought. It was then predicted that the presence of an additional *ortho* chlorine substituent could facilitate the coupling reaction by sterically hindering the pyridyl nitrogen's ability to coordinate. In order to test this hypothesis 2,6-di-chloro-4-tert-butylpyridine **276** was required. The synthesis and subsequent reaction of this compound is discussed in the next section.

3.1.3.3 Preparation of 4'-di-methyl-amino-4-tert-butyl-6-chloro-2,2'-bipyridine

3.1.3.3.1 Preparation of 2,6-di-chloro-4-tert-butylpyridine

In an analogous fashion to that described above, treatment of *N*-oxide **274** with $POCl_3$ afforded**,** following chromatography, 2,6-di-chloro-4-tert-butylpyridine **276** in 70% yield (**Scheme 62**)[98].

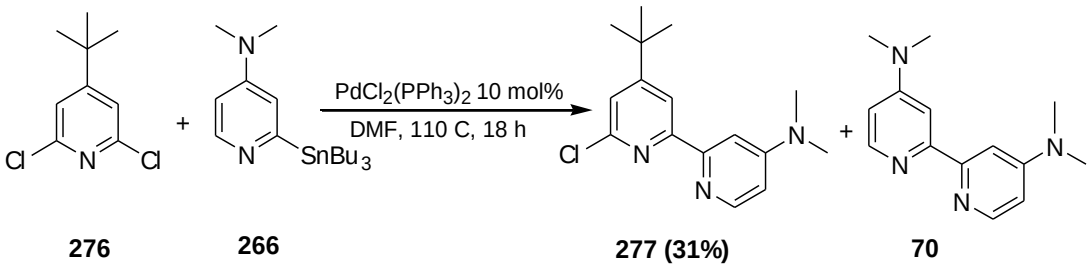


274 **276 (70%)**

Scheme 62: Preparation of 2,6-di-chloro-4-tert-butylpyridine 276[98]

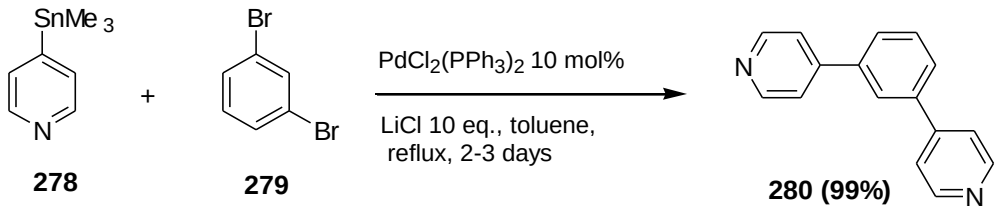
Confirmation of this product was obtained by GC-MS, which showed a peak at Rt = 7.1 min with the correct isotopic ratio 1:6:9 for two chlorine atoms. Furthermore, the ^1H NMR spectrum showed a characteristic 3,5-H signal at δ = 7.18 and lacked the characteristic 6-H signal at δ = 8.26. With di-chloropyridine **276** available it was

attempted to generate the desired bipyridine **277.** Following the cross-coupling conditions described above (**Section 3.1.3.2, entry 2, Table 29**), complete consumption of starting material **276** was observed**.** Analysis of the crude mixture by LC-MS, showed peaks at Rt = 2.3 and 1.2 min with *m/z* = 289 ([M (^{35}Cl)]$^{+}$) for **277** and m/z = 242 ([M]$^{+}$) for **70** respectively, indicated that the crude mixture contained a mixture of the desired bipyridine together with bis amine arising from homocoupled stannane in a ratio of 86:14 (**Scheme 63**).

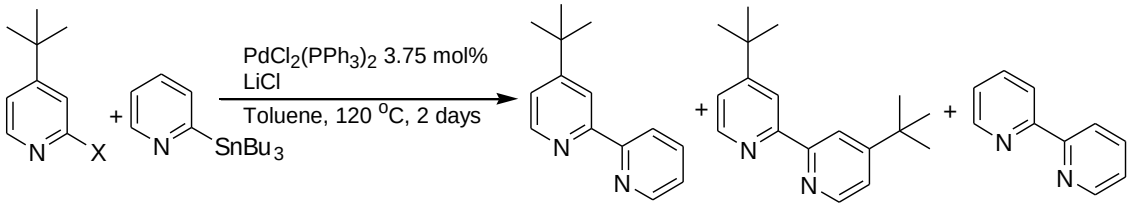


Scheme 63: Preparation of 4'-di-methyl-amino-4-tert-butyl-6-chloro-2,2'-bipyridine 277

Following chromatography, 4'-di-methyl-amino-4-tert-butyl-6-chloro-2,2'-bipyridine **277** was isolated in a yield of 31%. The low yield of **277** may be due to difficulties purifying the product. Extraction of the crude mixture with HCl was necessary to separate the tin salts from the product prior to chromatography**.** In conclusion the introduction of the 6-chloro-substituent enabled the successful synthesis of the desired bipyridine **277**. However the low overall yield of the coupling step necessitated a change in strategy. Fujita *et al*. have reported that the addition of metal salts (LiCl) can enhance the efficiency of Stille cross-coupling reactions (**Scheme 64**).[101] To explore this possibility a model reaction was conducted to prepare the bipyridine product, using LiCl to aid the transmetallation (**Table 30**).



Scheme 64: Preparation of 4-[3-(4-pyridinyl)-phenyl]-pyridine 281[101]



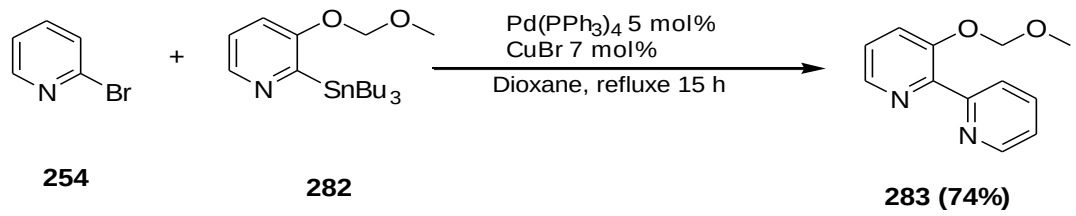
252 (X= Br)
265 (X= Cl)
272
281
22
38

entry No	X	Conv[a] %	ratio[a] (281:22:38)	(281) yield%
1	Br	100	80:10:10	40
2	Cl	100	77:12:11	32

[a] ratio determined by LC-MS

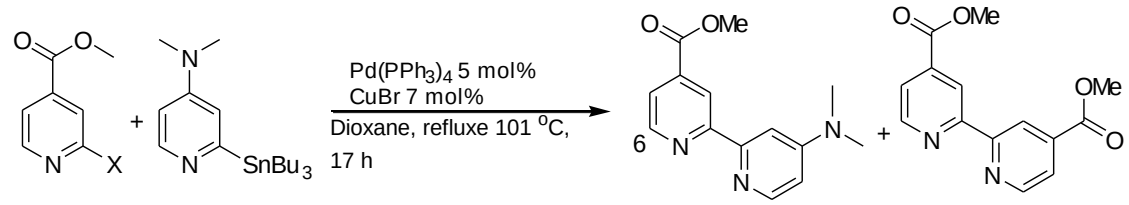
Table 30: Preparation of 4-tert-butyl-2,2'-bipyridine 281

After extraction of the crude mixture with HCl (6 M) to remove tin salts, purification by reversed phase chromatography, afforded a 40% yield of the desired bipyridine product **281** (M^+ peaks at Rt = 2.5 min with *m/z* = 212 ($[M]^+$)), when starting from 2-pyridyl bromide. The use of Cu salts has also been reported to enhance efficiency through promotion of the transmetallation step (**Scheme 65**).[102] This proved to be more successful, enabling the isolation of unsymmetric bipyridine **285** in 50% yield, following purification by column chromatography (**Table 31**).



254 **282** **283 (74%)**

Scheme 65: Stille cross-coupling reaction using CuBr[102]



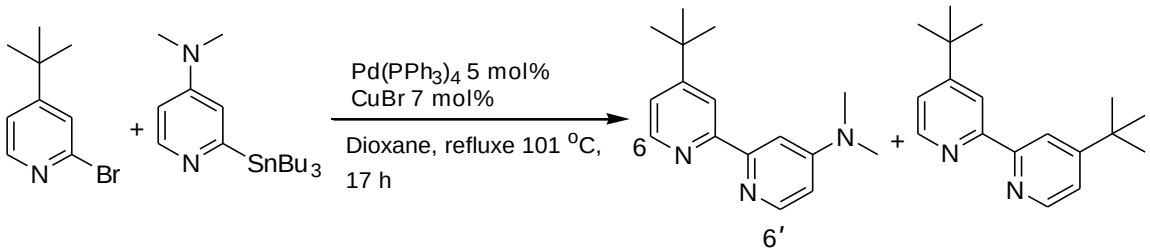
151 (X= Cl)
284 (X= Br)
266
285 6′ **286**

entry No	X	Conv.[a] %	Ratio (285:286)[a]	Yield% (285:286)
1	Cl	100	6.5:1.0	50:2
2	Br	100	11.0:1.0	50:2

[a]conversion and ratio determined by ^{1}H NMR

Table 31: Preparation of bipyridine 285

Following the same precedent, 2-bromo-4-tert-butylpyridine **252** and 4-di-methylamino-2-tri-butylstannylpyridine **266** were reacted in a similar fashion to afford bipyridine **250 in 47%** isolated yield (**Scheme 66**).



252 **266** **250** 6′ **22**

Conv. (%)[a]	Ratio (250:22)[a]	(250) Yield%
100	11.0:1.0	47

[a]conversion and ratio determined by ^{1}H NMR

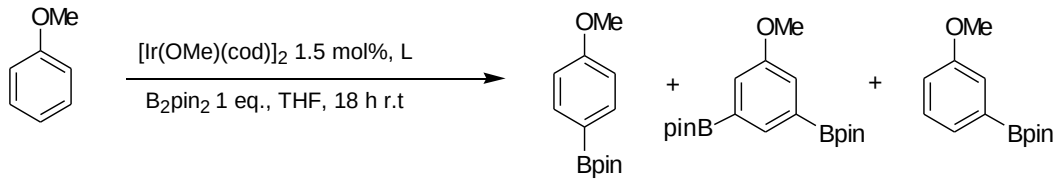
Scheme 66: Preparation of bipyridine 250

Having successfully prepared unsymmetrical bipyridines **250** and **285,** the next stage was to compare their efficacy as ligands in the borylation reaction with that of commercially available dtbpy **22**. This is discussed in the next section.

3.2 Ligands evaluation

3.2.1 Borylation of anisole

In order to compare the relative activity and regioselectivity of ligand **250** with the literature gold standard, dtbpy **22**, used in most borylation reactions, the initial experimental was to borylate anisole using [Ir (OMe) (cod)]$_2$ **21** and B_2pin_2.



35 **15** **287** **288**

entry No	Ligand (L)	Conv.[a] %	ratio[a] (15 & 288:287)	ratio[b] (15:287:288)
1	250	90	66:24	1.0:0.6:4.3
2	22	99	66:33	1.0:1.0:4.2

[a]conversion and ratio were determined by GC-MS
[b]ratio was determined by ^{1}H NMR

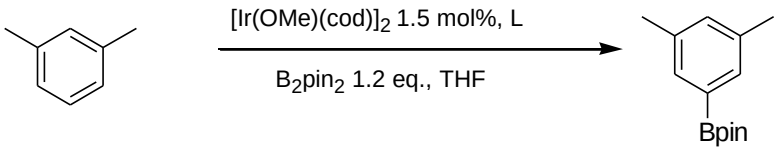
Table 32: Borylation of anisole using ligands 250 and 22

The reactions in Table 7 were carried out at room temperature for 18 h and analysed by GC-MS and ^{1}H NMR spectrums. In both cases near complete consumption of starting material was obtained, affording a mixture of mono- and bis-borylated products (**Table 32**). Over this time frame this suggested that the activity of ligand **250**

is comparable to the activity of dtbpy **22**. However a more detailed kinetic analysis of the progress of the reaction was not undertaken. Regioisomeric analysis by ^{1}H NMR spectroscopy followed the assignments previously described by Tajuddin[10] and suggested that **250** afforded decreased amounts of *meta* borylation. The reasons for this are not immediately apparent, but suggest that other nonsymmetrical ligands may provide a solution to the regiocontrol challenge. Similar analysis by GC-MS was attempted but in the absence of calibrated response factors proved more challenging to interpret. For example, integrating the M^{+} peaks at Rt = 15.1-16.0 min and 22.1-22.6 min with *m/z* = 234 ($[M]^{+}$) and 360 ($[M]^{+}$), suggested that the crude mixture contained 3 mono and 3 bis-borylated products in similar ratios for both ligands. In order to simplify the analysis the test system was modified to use 1,3-di-substituted benzene derivatives.

3.2.2 Borylation of m-xylene

As above, m-xylene **19** was borylated using 1.2 eq of B_2pin_2 at r.t and 80 ^{o}C with reaction conversions being determined by ^{1}H NMR analysis using undecane as a standard (**Table 33**).



19 **23**

entry No	Ligand (L)	T ^{o}C	conv%[a] 2 h	4 h	6 h	24 h	72 h	168 h
1	250	r.t	----	-----	----	19	31	49
2	22	r.t	----	----	-----	19	51	79
3	285	r.t	-----	----	-----	13	19	29
4	250	80	66	85	90	----	----	----
5	22	80	85	88	89	-----	----	----
6	285	80	34	38	43	-----	----	----

[a]conversion determined by ^{1}H NMR

Table 33: Borylation of m-xylene using 250, 22 and 285

In all cases, as expected, only a single monoborylated product was observed in GC-MS (Rt = 6.8 min; *m/z* = 232 ($[M]^{+}$)). Of the three ligands evaluated **22** showed the highest activity at room temperature. Interestingly the formation of the borylated product **23** was slower when ligand **250** was used instead of dtbpy **22**, suggesting that the formation of the active complex was slower. Consistent with this, when the reactions were heated at 80 ˚C, the difference between **250** and **22** was less pronounced. The more electron withdrawing ligand **285** was significantly less effective to coordinate the iridium catalyst suggesting that the linker should not contain EWGs directly attached to the 4–position.

3.2.3 Borylation of methyl-(2-methyoxy)-benzoate

Since the borylation of anisole **35** suggested that an unsymmetrical ligand could modulate the activity, it was of interest to further probe this observation. In earlier work the room temperature borylation of 2-methoxy-methylbenzoate **57** had been shown to give a **289:290** mixture of regioisomers [10] and was thus a good substrate to verify this observation (**Table 34**).

57 **289** **290**

entry No	Ligand (L)	Conv. (%)[a] (289&290)	ratio[b] (289:290)
1	250	98	7.1 : 1.0
2	285	78	5.4 : 1.0
3	22	97	6.5 : 1.0

[a]conversion determined by GC-MS
[b]ratio determined by ^{1}H NMR

Table 34: Borylation of methyl-(2-methoxy)-benzoate using 250, 22 and 285

Reflecting the higher reactivity of this substrate all the ligands afforded good conversion of the substrate to the corresponding arylboronate at r.t. Consistent with the results from the borylation of anisole regioisomeric analysis by ^{1}H NMR spectroscopy showed marginal difference in selectivity in the borylation reaction when using ligand **250** compared to dtbpy **22**.

3.3 Synthesis and evaluation of 2-(4'-di-methylamino-2,2'-bipyridine-4-yl)-N-methylacetamide)

From the work described above (**Section 3.2.2, Table 33**), it was clear that the presence of an EWG directly attached to the bipyridine was not desirable. Consequently it was decided to prepare bipyridines with a reversed amide linker attached to 4-amino-pyridine. The initial target was therefore chosen to be the 2-(4'-di-methylamino-2,2'-bipyridine-4-yl)-*N*-methylacetamide **296**. Similar structures have been prepared before, utilising the Stille cross-coupling reaction of 2-chloro-pyridines **151** with 2-tri-butylstannylpyridine **266** (**Section 3.1.3.3.1**, **Table 31**). Adopting this strategy (**Figure 27**) the initial goal became the preparation of the two precursors *N*-(2-chloro-pyridin-4-yl)-*N*-methyl-acetamide **294** and 4-di-methylamino-2-tri-butylstannylpyridine **266**.

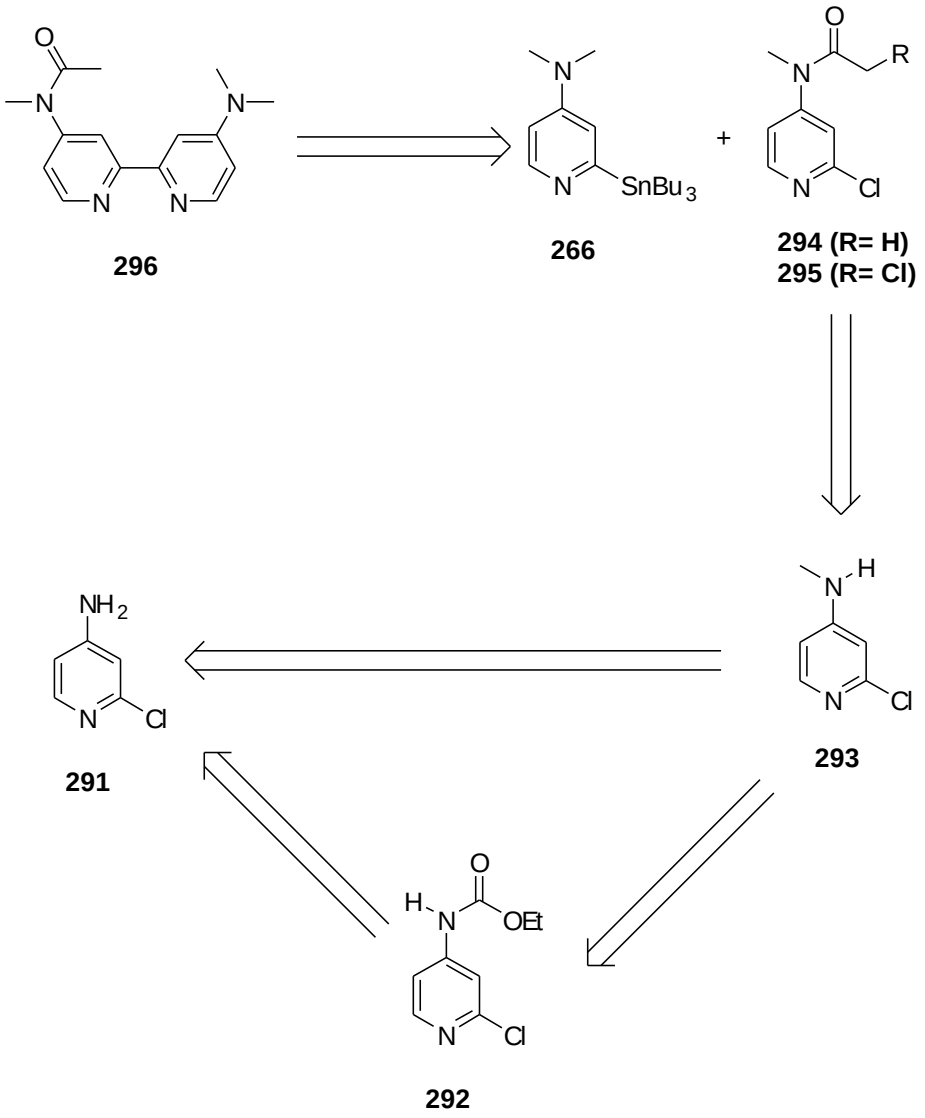
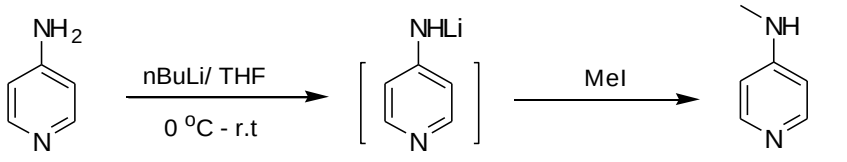


Figure 27: Retrosynthetic analysis of 296

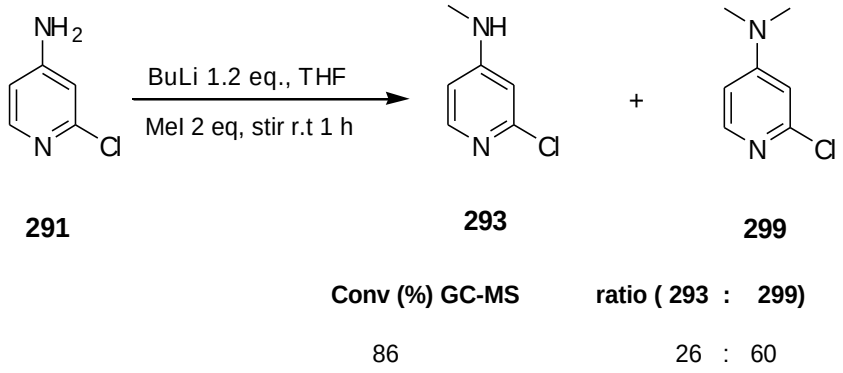
3.3.1 Preparation of 2-chloro-4-(*N*-methylamino)-pyridine



297 **298 (74%)**

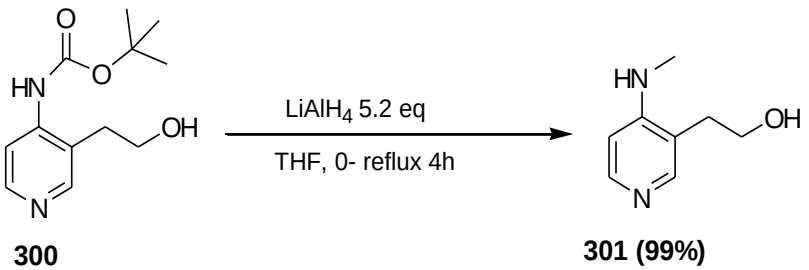
Scheme 67: Preparation of *N*-methyl-4-aminopyridine[103]

Based on the precedent established by Singh *et al.* (**Scheme 67**),[103] 2-chloro-4-(*N*-methylamino)-pyridine **293** was prepared through the addition of n-BuLi to 2-chloro-4-aminopyridine **291** at 0 °C and trapping of the resultant anion with methyl iodide **224** at room temperature (**Scheme 68**).



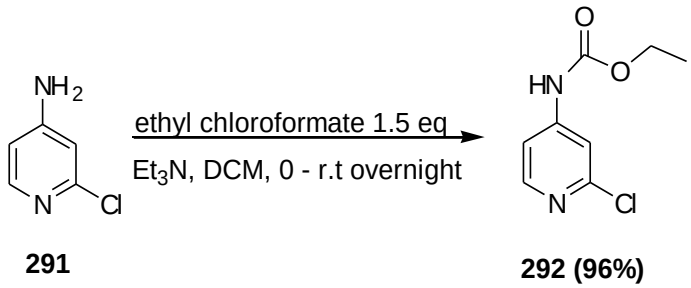
Scheme 68: Preparation of 2-chloro-*N*-methyl-4-aminopyridine 293

Although this reaction gave good conversion of starting material **291** (86%), di-alkylation to the undesired side product **299** was problematic. Consequently an alternative pathway was sought, and a survey of the literature revealed that the similar 4-(*N*-methylamino)-pyridine **301** can be formed by reduction of carbamate **300** using $LiAlH_4$ in THF (**Scheme 69**).[104]



Scheme 69: Preparation of 4-(*N*-methylamino)-pyridine 301[104]

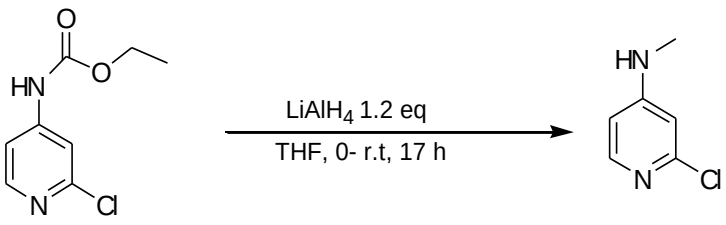
In order to explore this approach the desired carbamate **292** was readily prepared in excellent yield following literature protocols combining 2-chloro-4-aminopyridine **291** and ethyl chloroformate in DCM at room temperature (**Scheme 70**).[105] Confirmation of this product was obtained from a molecular ion peak in the GC-MS trace at Rt= 8.3 min *m/z* = 202 ([M (^{37}Cl)]$^+$), 200 ([M (^{35}Cl)]$^+$) coupled with the characteristic ethyl signals at δ = 4.2 and δ = 1.3 for the ethyl carbamate and a downfield shift in the *N*-H signal to δ=7.6 in the ^{1}H NMR spectrum. Finally a peak at 1736 cm^{-1} in the IR spectrum confirmed the formation of the carbamate (C=O stretch).



291 **292 (96%)**

Scheme 70: Preparation of carbamate 292

In order to generate the desired mono-methyl amine it was necessary to next reduce the carbamate and following Spivey *et al.*[104], carbamate **292** was treated with $LiAlH_4$ in THF at room temperature to afford, following chromatography, the desired methylamine **293** in 76% yield (**Scheme 71**).



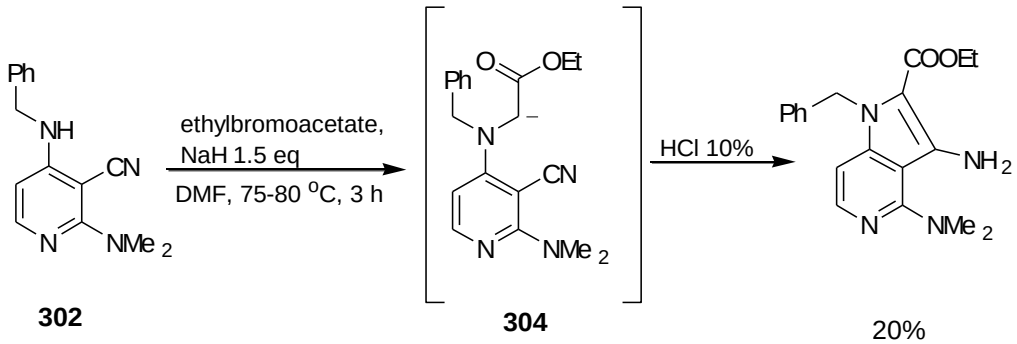
292 **293 (76%)**

Scheme 71: Preparation of 293

Confirmation of a successful reduction was obtained from the ^{1}H NMR spectrum which showed a characteristic methyl signal at δ = 2.8 ppm coupled with a shift to lower frequency for the *N*-H signal (δ=4.9 ppm) consistent with the reduction of the carbonyl group. Finally conformation for the retention of the chloro substituent was obtained by GC-MS that showed a peak at Rt= 6.9 min with the expected Cl isotope pattern *m/z* = 144 ([M (^{37}Cl)]$^{+}$, 34%), 142 ([M (^{35}Cl)]$^{+}$, 100%). With *N*-methylaminopyridine **293** available the next task was to attach a suitable linker group. This is discussed in the next section.

3.3.2 Preparation of *N*-(2-chloropyridin-4-yl)-*N*-methylacetamide derivatives

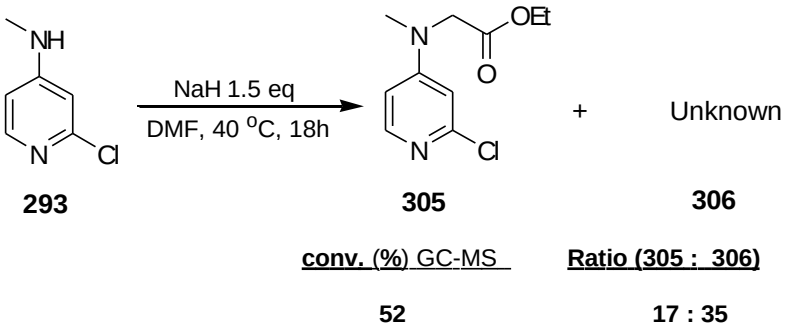
The first approach was to combine mono-methylamine **293** with ethylhaloacetate. According to procedure from Evstratova *et al.*[106] a similar compound **304** could be prepared by alkylation of 2-di-methylamino-3-cyano-4-benzylaminopyridine **302** with ethylbromoacetate **303** in presence of NaH as base (**Scheme 72**).



302 **304** 20%

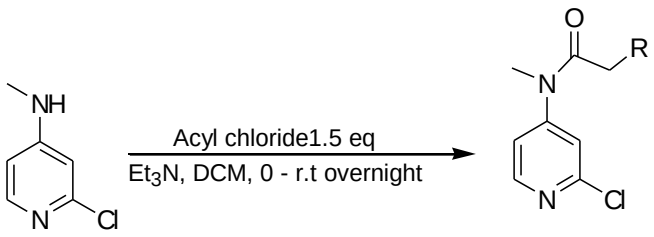
Scheme 72: Alkylation of sec amine[106]

Following this precedent, heating of methylamine **293** with ethyl bromoacetate **303** in DMF at 40 ^{o}C (**Scheme 73**) afforded [(2-chloropyridine-4-yl)-methylamino]-acetic acid ethyl ester **305**.



Scheme 73: Preparation of [(2-chloropyridine-4-yl)-methylamino]-acetic acid ethyl ester

However, the conversion of the starting material **293** (GC-MS analysis) was low and there was a significant amount of an unknown byproduct **306** (10.6 min, *m/z* = 286) formed. Attempts to improve the yield of **305** by using Bu_4NI and Cs_2CO_3 in DMF at 100 ^{o}C or replacing the ethylbromoacetate **303** with glutaric anhydride were not successful. The low yield of the desired product **305** may be due to the conjugated nature of the amine, which lowers reactivity. Switching to the more electrophilic acyl chloride successfully overcame this problem enabling the isolation of **294** and **295** in 42% and 90% yield respectively (**Table 35**).

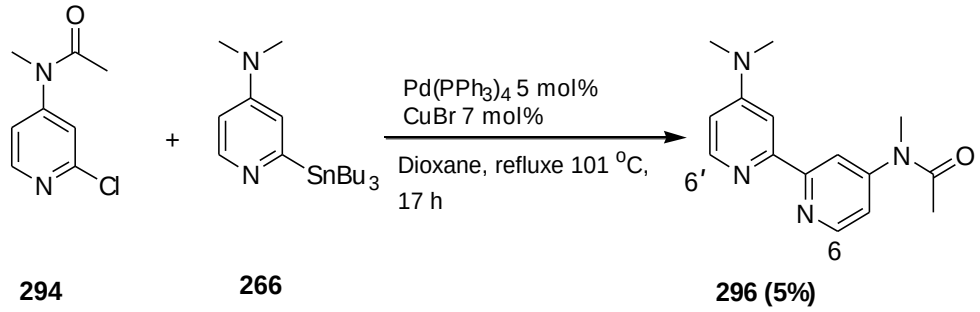


293

Prod No	R	Yield%
294	H	42
295	Cl	90

Table 35: Preparation of acetamide 294 and 295

In both cases formation of the amide was ascertained from the IR spectrum in which a peak at 1650-70 cm^{-1} (C=O stretch) could be observed. Confirmation of the pyridine **294** was obtained by GC-MS analysis, which showed a peak at Rt = 7.1 min [*m/z* = 186 ([M (^{37}Cl)]$^+$, 8%), 184 ([M (^{35}Cl)]$^+$, 25%). Similarly formation of amide **295** was also confirmed by GC-MS, which showed a peak with Rt = 8.4 min with the correct isotopic ratio 1:6:9 of di-chlorine [*m/z* = 222 ([M (^{37}Cl,^{37}Cl)]$^+$, 6%), 220 ([M (^{35}Cl,^{37}Cl)]$^+$, 35%), 218 ([M (^{35}Cl,^{35}Cl)]$^+$, 54%)]. With **294** in hand, synthesis of 2-(4'-Di-methylamino-2,2'-bipyridine-4-yl)-N-methylacetamide **296** was undertaken, using the procedure optimized for the syntheses of bipyridines **285** and **250 (Section 3.1.3.3.1, Table 31)**. However, this proved very difficult to purify, ultimately producing a very low yield of isolated material (5%) (**Scheme 74**). Characterisation of the product was complicated by the presence of amide rotamers but confirmation of the molecular formula [$C_{15}H_{19}N_4O$] was obtained by HRMS analysis, which showed the correct mass 271.1554, ([MH]$^+$ requires M, 271.1559).



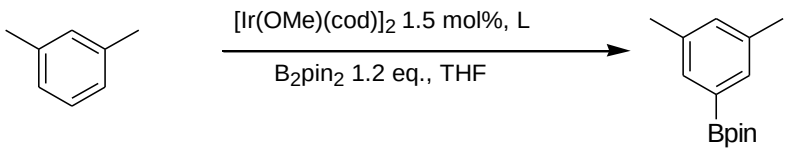
294 **266** **296 (5%)**

Scheme 74: Preparation of bipyridine 296

Although the difficulty in purification resulted a low yield of the bipyridine **296,** sufficient material could be prepared to enable the testing of the activity of this ligand. This is discussed in the next section.

3.3.3 Borylation of m-xylene using bipyridine 296 as ligand

Following the protocols established above (**Section 3.2.2**), **296** was used as a ligand in the borylation of m-xylene at r.t and 80 ˚C, enabling a comparison with ligand **285** (**Section 3.2.2, Table 33**). Based on the conversion of starting material, **296** showed higher activity (**Table 36, entry 3**), confirming the hypothesis that the linker at C-4 must not contain an electron withdrawing group directly attached to the pyridyl ring.



19 **23**

entry No	Ligand (L)	T °C	conv%[a] 2 h	4 h	6 h	24 h	72 h	168 h
1	296	r.t	-----	-----	----	26	41	69
2	285	r.t	----	----	-----	13	19	29
3	296	80	50	67	75	----	----	----
4	285	80	34	38	43	-----	----	----

[a]conversion determined by ^{1}H NMR

Table 36: Comparison of Ligands 285 and 296

3.4 In conclusion

In this work, a range of 2-functionalised pyridines were synthesised using Fort's protocol. Asymmetrical bipyridines were successfully prepared in a Stille cross-coupling reaction using CuBr to aid transmetallation. These bipyridine ligands were evaluated with different substrates to explore the activity and selectivity compared with the active dtbpy ligand in a borylation reaction. Ligands **22** and **250** showed comparable activity in the borylation of m-xylene after heating in an oil bath at 80 °C for 6 h, while **285** showed less activity in the borylation of substrates due to the elctron-withdrawing group at the 4-position of the pyridine ring. In addition, a method was discovered to prepare bipyridine **296** with a reversed amide linker, which could then be used to attach the ligand to a polymer. Ligand **296** was similarly prepared to ligands **250** and **285** using a copper salt Unfortunately, concurrent with these studies Jones *et al.* published a paper, showing the synthesis of a silica supported Iridium catalyst **187** with

a bipyridine ligand (**Figure 16**).[74] In this report they demonstrated that the silica supported iridium catalyst is stable in air and can be recovered by simple filtration and re-used for further borylation reactions. This catalyst showed good activity in the borylation of various arenes. Therefore alternative ligands were explored. Based on Hartwig's reports[107] of the high activity of phenanthroline derivatives as ligands in the borylation reaction, attention turned to the preparation of a modified phenanthroline ligand, which could be used in the synthesis of a polymer supported iridium catalyst. This work is described chapter 5.

Chapter 4

4 Multidirectional synthesis of pyridines

4.1 Introduction

Pyridines are an important motif in agrochemicals and pharmaceuticals.[108] For example Henke *et al.* reported that 2-amino-4,6-di-arylpyridine derivatives may have efficacy in the treatment of diseases caused by the loss of estrogen (**Figure 28**).[109] Common methods for the preparation of 2,4,6-substituted pyridines use three halide groups on pyridine which react in turn to produce the desired pyridines along with many halogenated side products.[110] Therefore, a key solution for this problem is to borylate substituted-pyridine as previously studied in the group. Tajuddin reported[10] that blocking 2- and 4-positions of pyridine such as methyl-2-chloroisonicotinate **151** led to *ortho* borylated product **152**.

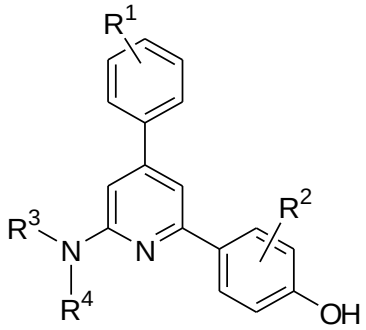


Figure 28: Preparation of 2-amino-4,6-di-arylpyridine derivatives[109]

Following this strategy, the aim of this work was to prepare functionalized pyridine building blocks, which can be further used in the multidirectional synthesis of substituted pyridine derivatives, using Suzuki-Miyaura coupling of aryl boronate esters with a range of aryl halides and subsequently aromatic nucleophilic substitution with a range of amines (**Figure 29**).

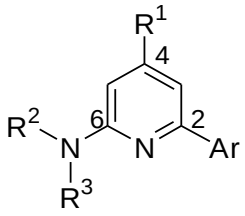


Figure 29: Preparation of 2,4,6-substituted pyridine derivatives

4.1.1 Preparation of 2,4,6-substituted pyridine derivatives

Retrosynthetic analysis of the desired 2,4,6-substituted pyridine derivatives **320-327**, showed that these products could be prepared through two routes (**Figure 30**). The first route involves the reaction of 6-chloropyridine derivatives **310,313,318-319** with a range of amine derivatives via a S_NAr reaction. 2-aryl-4-substituted-6-chloro pyridine derivatives **310-319** can be prepared by coupling of arylboronate esters **152, 307** and **309** with a range of aryl halides in a Suzuki-Miyaura cross-coupling reaction. Arylboronate esters (**152, 308** and **309)** can be synthesized by the borylation of 2-chloro-4-substituted pyridine derivatives **151, 265** and **307** using the active catalyst tris-boryl species $Ir(Bpin)_3(dtbpy)$. The second route to prepare compound **320,** involves the coupling of 2-borylated pyridine **329** with 4-iodonitrobenzene in a Suzuki-Miyaura cross coupling. 2-Borylated pyridine derivatives **329** can be prepared through two steps, starting with a S_NAr reaction of 2-chloro-pyridine **307**, followed by the standard borylation procedure using an Ir catalyst. Borylation of 2-chloro-4-substituted pyridine derivatives **152, 308** and **309** will be discussed first in the next section.

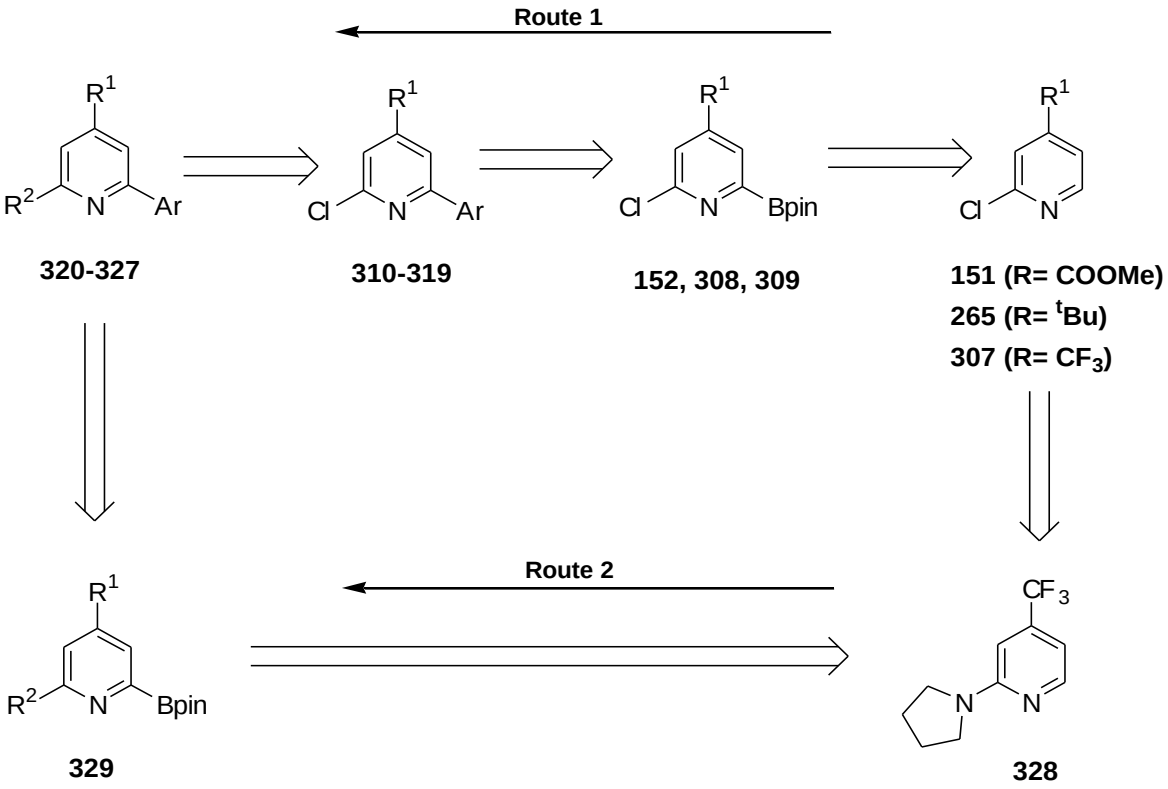
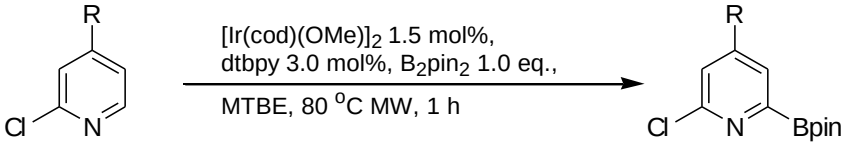


Figure 30: Retrosynthetic analysis of multidirectional pyridine derivatives

4.1.1.1 Borylation of 2-chloro-4-substituted pyridine derivatives

A survey of the literature revealed that 6-borylated product **152** can be prepared using the standard borylation procedure with methyl-2-chloroisonicotinate **151** (**Scheme 24**, **chapter 1**).[10] Following this protocol, carrying out the borylation at 80 °C for 1 h in a μW reactor, a range of 6-borylated products **152, 308** and **309** was obtained (**Table 37**).



151 (R= COOMe)
265 (R= ^{t}Bu)
307 (R= CF_3)

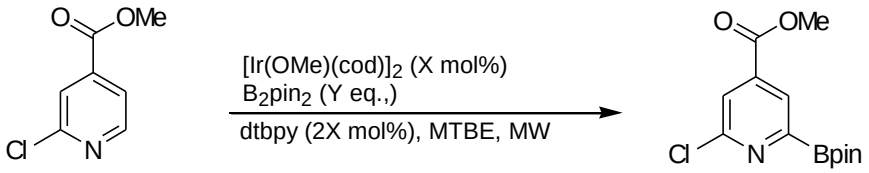
R	Ar-Bpin No	Rt min:(m/z)[a]	Conv.[a] %
^{t}Bu	**308**	8.9: 297 [M, ^{37}Cl]$^{+}$, 33% 295 [M, ^{35}Cl]$^{+}$,100%	88
CF_3	**309**	6.5: 309 [M, ^{37}Cl]$^{+}$, 32% 307 [M, ^{35}Cl]$^{+}$, 100%	88
COOMe	**152**	9.2: 299 [M, ^{37}Cl]$^{+}$, 33% 297 [M, ^{35}Cl]$^{+}$, 100%	68

[a]conversions determined by GC-MS analysis

Table 37: Borylation of 2-chloro-4-substituted pyridine derivatives

Although both **151** and **307** have electron-withdrawing groups, GC-MS analysis unexpectedly showed a lower conversion for **151** compared to **307**. Because of the importance of the ester group of **152**, which could be used to further functionalize at the 4-position of the pyridine ring, we attempted to increase the yield of 6-borylated product **152**. In order to explore the best conditions for the borylation, a fractional design of experiments approach was employed. Five factors were suggested that could influence the borylation of methyl-2-chloroisonicotinate. These were the mol% of $[Ir(OMe)cod]_2$, the equivalents of B_2pin_2, the temperature, the time and the concentration (**Table 38**). To explore all combinations of these variables at two settings would require a minimum of 32 experiments. This was not possible in the time available and consequently a fractional approach was adopted in which a quarter fraction (**8 experiments**) were undertaken with two control experiments at the mid-

point values. This gave the results shown in (**Table 38**). Analysis of each set of variable at both high and low settings (**Figure 31**) suggested that the effect of time, concentration and diboron stoichiometry had relatively little effect on conversion but that higher Ir loading and temperatures afforded better yields. Consequently a final experiment was identified to give the most efficient conditions for the borylation of 2-chloropyridine **151** (**Scheme 75**).

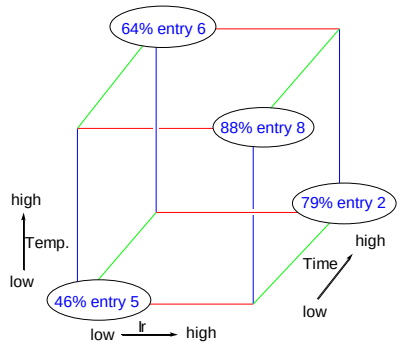


151 **152**

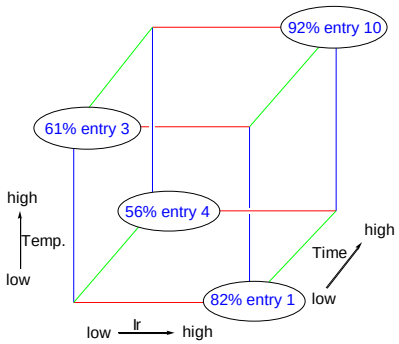
entry No	Ir-cat (mol%)	B_2pin_2 (eq.)	Time (min)	T (^oC)	Conc.	Conv. (%)[a]
1	5.0	1.5	30	60	0.25	82
2	5.0	0.9	90	60	0.25	79
3	1.0	1.5	30	100	0.25	61
4	1.0	1.5	90	60	0.75	56
5	1.0	0.9	30	60	0.75	46
6	1.0	0.9	90	100	0.25	64
7	3.0	1.2	60	80	0.5	79
8	5.0	0.9	30	100	0.75	88
9	3.0	1.2	60	80	0.5	81
10	5.0	1.5	90	100	0.75	92

[a]conversions determined by GC-MS

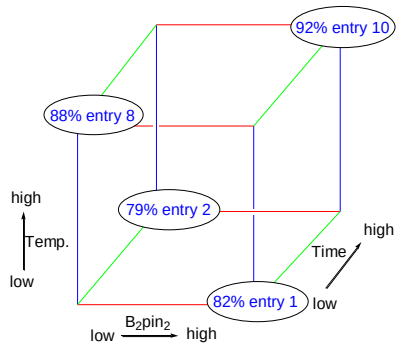
Table 38: Borylation of 2-chloroisonicotinate using different conditions



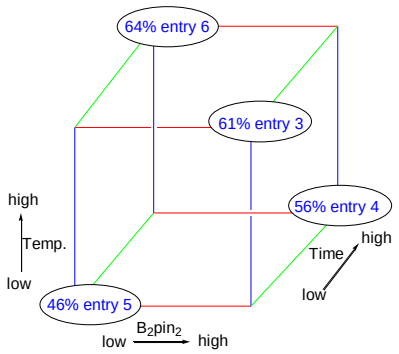
Constant B_2pin_2 =0.9



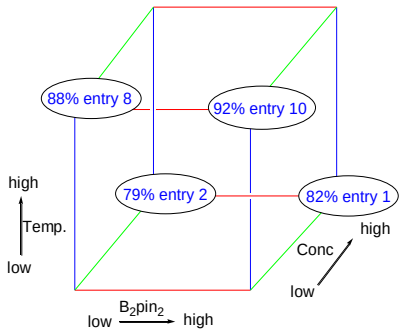
Constant B_2pin_2 =1.5



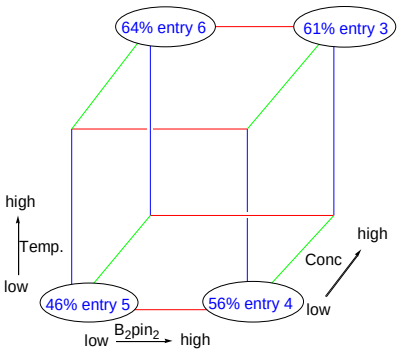
Constant Ir mol% =5



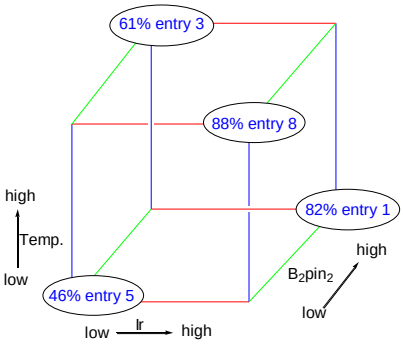
Constant Ir mol% =1



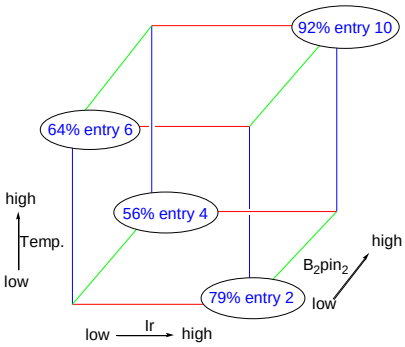
Constant Ir mol% =5



Constant Ir mol% =1

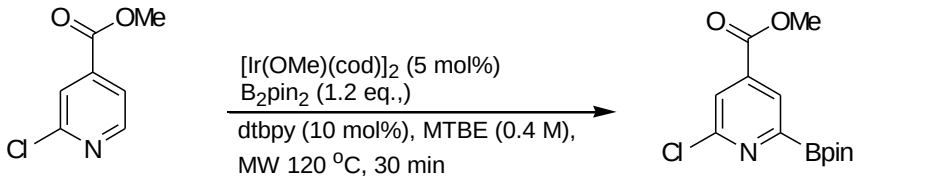


Constant time= 30 min



Constant time= 90 min

Figure 31: Fractional design of borylation 2-chloropyridine 151



151

152 (95% conv. by GC-MS)

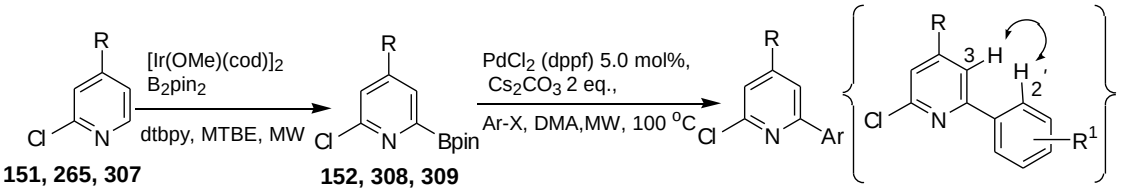
Scheme 75: The best condition to the borylation of pyridine 151

Using fractional design of borylation 2-chloropyridine **151** suggested that the yield of 6-borylated product **152** increased by increasing the mol% of $[Ir(OMe)cod]_2$ and temperature. Entries **7** & **9** in (**Table 38**) had identical conditions and showed very similar conversions, suggesting that the method is consistent. With the 6-borylated products in hand, Suzuki Miyaura cross-couplings were carried out directly, without further purification, with aryl halide derivatives. This will be discussed in the next section.

4.1.1.2 Preparation of 2-(aryl substituted)-heteroaromatics

The first example was to directly coupling of pyridine **152**, without further purification, with a range of aryl halides using 5.0 mol% of $PdCl_2(dppf)_2$ and Cs_2CO_3 in DMA at 120 ^oC in a μW (**Table 39**). Product **310**, was obtained via a cross coupling reaction with 4-iodo-nitrobenzene. GC-MS showed a 100% conversion of SM and the M^+ peak was observed at Rt = 11.7 min with *m/z* = 294 ([M (^{37}Cl)]$^+$, 33%), 292 ([M (^{35}Cl)]$^+$, 100%). Following chromatography, the desired product **310** was isolated in 45% yield. This compound substitution at C-2 was confirmed by a NOESY correlation between 2'-H and 3-H. In a similar fashion 2-aryl-4-substituted-6-chloropyridine derivatives **311-319**

could be prepared in 10-67% yield. The low yields for product **310** could be due to the rather low conversion of 68% of methyl-2-chloroisonicotinate **151** to the crude arylboronate. However, for not obvious reason the yield for product **311** did not improve, when different borylation conditions were used.



151, 265, 307 **152, 308, 309**

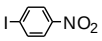
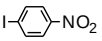
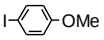
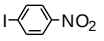
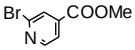
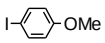
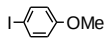
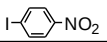
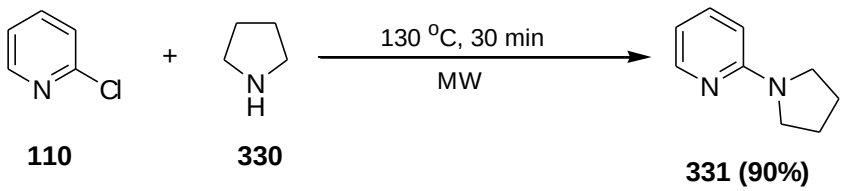
Prod No	R	Ar-x (eq.)		Borylation condition	Time h	yield%
310	COOMe		1.5	Table 37	3	26
310	COOMe		1.5	Scheme 75	3	45
311	COOMe		1.5	Scheme 75	3	10
312	COOMe		1.5	Scheme 75	3	48
313	^{t}Bu		1.5	Table 37	3	40
314	^{t}Bu		1.5	Table 37	3	66
315	^{t}Bu		1.5	Table 37	3	67
316	^{t}Bu		1,5	Table 37	3	42
317	^{t}Bu		1,5	Table 37	3	44
318	**CF_3**		**1.5**	Table 37	3	36
319	**CF_3**		**1.5**	Table 37	3	58

Table 39: Coupling of 2-chloro-4-substituted-6-borylated products with arylhalides

With the 2-aryl-6-chloropyridine derivatives in hands, it was decided to form a C-N bond in a S_NAr reaction. This is discussed in the next section.

4.1.1.3 Preparation of [6-(4-nitrophenyl)-4-tri-fluoromethylpyridine-2-yl]amine derivatives

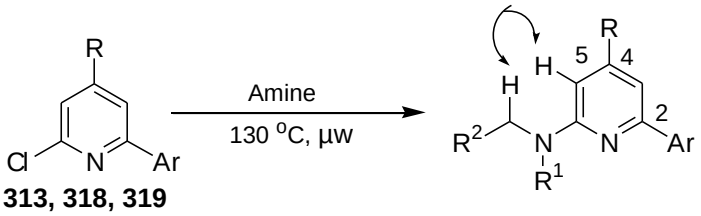
A survey of the literature revealed that similar products could be prepared through heating an amine with 2-chloropyridine **110** at 130 ^{o}C for 30 min in the μW (**Scheme 76**).[111]



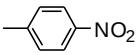
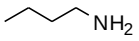
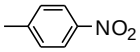
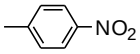
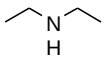
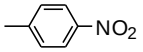
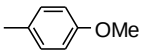
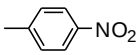
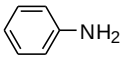
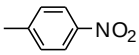
110 **330** **331 (90%)**

Scheme 76: Preparation of 2-pyrrolidinylpyridine[111]

Following this precedent, a range of examples could be prepared by reacting 6-chloropyridine derivatives **310**,**313**,**318** and **319** with a range of amines in a S_NAr reaction (**Table 40**) (**Scheme 77**).

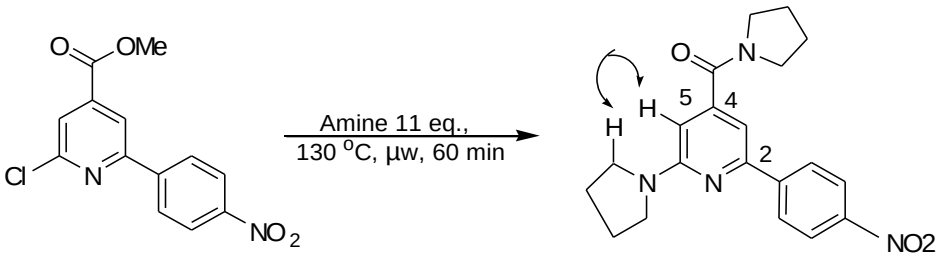


313, 318, 319

prod No	R	Amine	Amine (eq,)	Ar	T (min)	Yield%
320	CF_3		5.5		60	78
321	CF_3		5.5		60	75
322	CF_3		5.5		60	92
323	CF_3		29		360	61
324[a]	CF_3		5.5		30	20
325	^tBu		5.5		30	31
326	CF_3		5.5		60	0

[a]yield over three steps started with the borylation of 2-chloro-4-tertbutylpyridine

Table 40: Preparation of 2-aryl-4-substituted-6-alkylaminopyridine derivatives



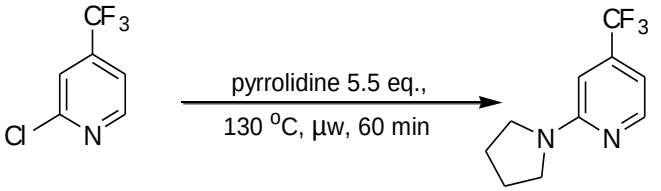
310 **327 (75%)**

Scheme 77: Preparation of [2-(4-nitrophenyl)-6-pyrrolidin-1-yl-pyridin-4-yl]-pyrrolidin-1-yl-methanone

Product **320** was prepared by reacting starting material **319** with pyrrolidine. GC-MS showed a 100% conversion with a peak at Rt = 12.1 min with *m/z* 337 ($[M]^+$, which indicated that the crude mixture contained the desired pyridine **320**. Following chromatography, the product **320** was isolated in 78% yield. Confirmation of this product was obtained by GC-MS, which lacked a signal with the isotopic ratio for a chlorine atom. Furthermore, the signal for the 5-H in the ^{1}H NMR spectrum moved to a slightly lower frequency δ =6.6 ppm. Additionally, the ^{1}H NMR spectrum showed a NOESY correlation between *N*-CH_2 and 5-H. In a similar fashion pyridine analogues **321-327** could be prepared in 20-92% yield. However the S_NAr reaction was not successful, when using aniline with 6-chloropyridine **319** and did not afford the product **326**. This may be due to the aniline not being a good nucleophile. In order to obtain compound **323** in good yield, an excess amount of diethylamine was used and a longer reaction time. This is due to the low boiling point of diethylamine compared with other amines. It was found that using excess of pyrrolidine with pyridine **310** not only resulted in a S_NAr reaction to generate a C-N bond, but also hydrolysed the ester to generate an amide **327** (**Scheme 77**). In order to find the best route to prepare pyridine derivatives, pyridine **320** was also prepared using route 2, the results are discussed in the next section.

4.1.1.4 Preparation of 4-tri-fluoromethyl-6-(N-pyrrolidinyl)-pyridine

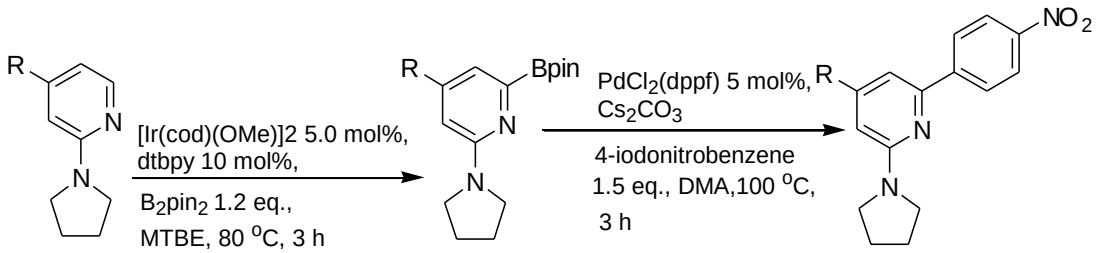
Following the second route above (**Section 4.1.1, Figure 30)** to prepare the 2,4-6-substituted pyridine derivatives, Following the S_NAr procedure applied above (**Scheme 76**), 4-tri-fluoromethyl-2-(*N*-pyrrolidinyl)-pyridine **328** was obtained in a 90% yield (**Scheme 78**).



307 **328 (90%)**

Scheme 78: Preparation of 4-tri-fluoromethyl-2-(*N*-pyrrolidinyl)-pyridine

In order to prepare the desired pyridine **320**, according to the route **2** (**Figure 30**), borylation of compound **328** was needed. Following the standard borylation procedure, described before (**Section 4.1.1.1, Table 37**), a 84% conversion of pyridine **328** was obtained by ^{1}H NMR analysis. Ar-Bpin **329** was coupled directly with 4-nitroiodobenzene to afford the desired pyridine **320** in 49% yield (**Scheme 79**).



328 (R = CF_3) **329 (84% by ^{1}H NMR)** **320 (49%)**

Scheme 79: Preparation of 4-tri-fluoromethyl-6-(*N*-pyrrolidinyl)-pyridine

4.2 Summary and Conclusions

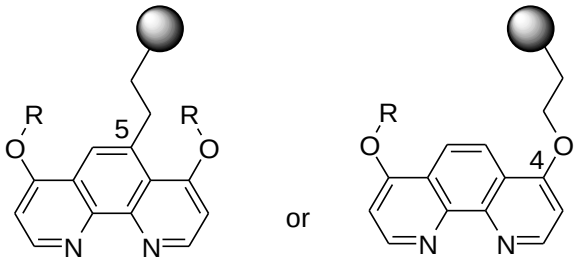
In this work, a range of multisubstituted pyridines was prepared over three steps in good yields. Both routes were effective for the preparation of the final pyridine **320**. For unclear reasons borylation of pyridine containing CF_3 and ^tBu at 4-position gave a better conversion of the starting material than with an ester group. Through fractional design of borylation reactions, it was found that increased loading of Ir-catalyst and higher temperature using microwave reactor led to greater conversion in the borylation of methyl-2-chloroisonicotinate **151**. An 82% conversion of **328** was achieved with a high loading of Ir catalyst and B_2pin_2 with heating in microwave reactor for 3 h. A number of bi-aryl compounds were successfully prepared using the Suzuki-Miyaura cross-coupling reaction. In the solvent-free S_NAr reaction, the aliphatic amines showed a better activity in the reaction compared with aromatic amines.

Chapter 5

5 Synthesis of phenanthroline ligand using in polymer supported iridium C-H borylation

5.1 Introduction

As described in section **1.1.4.3** above, owing to the reported high activity achievable, the use of phenanthroline-type ligand systems in supported C-H borylation was an attractive approach.[43,107] As with the bipyridine ligands discussed in **chapter 3,** the aim was to prepare modified phenanthroline derivatives that could be coupled to a suitable polymeric support (**Figure 32**). Ideally these ligands would contain bearing electron-donating groups as it was anticipated that these would unlock the highest activity. Therefore, ligand systems **332** and **333** were chosen as initial synthetic target for this aspect of the project. As before, it was of interest to compare the selectivity and activity of these phenanthroline derivatives in the borylation reaction with commercial available ligands such as 3,4,7,8-tetra-methyl-[1,10]-phenanthroline **66**.



332 **333**

Figure 32: Target Ligands

5.1.1 Preparation of 4,7-di-substituted-[1,10]-phenanthroline

A review of the literature revealed that 4,7-di-substituted-[1,10]-phenanthroline may be accessed by heating 1,2-bis-[(2,2-di-methyl-4,6-dioxo-1,3-dioxan-5-ylidenemethyl)-amino]-benzene derivatives **337, 340 and 341 (Figure 33).** Compound **337** may be prepared in turn, by heating phenylenediamine **334** with Meldrum's acid **335** in tri-methyl *ortho*formate **336** (**Scheme 80**).[112,113]

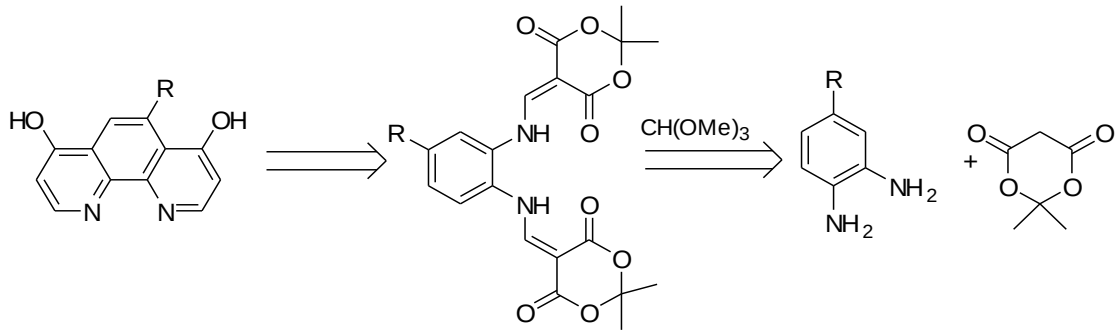
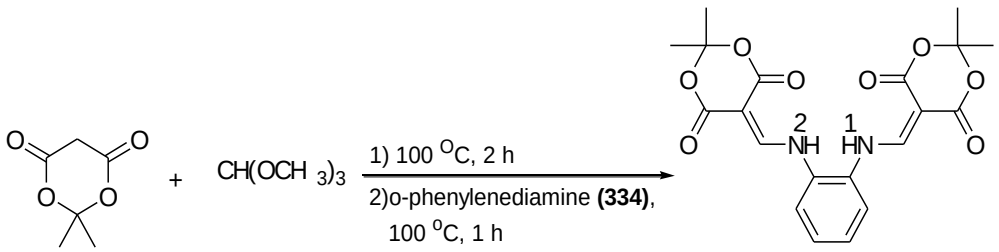


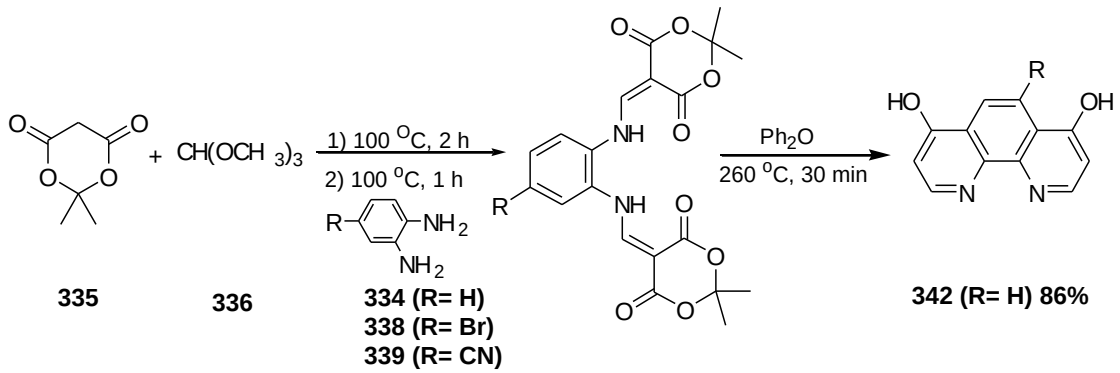
Figure 33: Retrosynthetic analysis of 4,7-di-hydroxy-[1,10]-phenanthroline[112,113]



Scheme 80: Preparation of 1,2-bis[(2,2-di-methyl-4,6-dioxo-1,3-dioxan-5-ylidenemethyl)-amino]-benzene[112]

Following this precedent, a number of substituted 1,2-bis-aminobenzene derivatives **337**, **340-341** were prepared (**Table 41**). The sequence proved straightforward, with

the desired products being accessed in acceptable yields, after washing with ether. Each intermediate was characterised using a combination of LCMS, IR and NMR spectroscopy.



335 **336** **334 (R= H)** **338 (R= Br)** **339 (R= CN)** **342 (R= H) 86%**

Comp. No	R	LC-MS Rt min, m/z	ATR	yield%
337	H	2.7, 854 $[M_2\text{-}H+Na]^+$	3264 (NH) 1725 (C=O)	82
340	Br	3.0, 1012 $[M_2H+Na, {}^{79}Br]^+$ 1014 $[M_2H+Na, {}^{81}Br]^+$	3165 (NH) 1724(C=O)	60
341	CN	2.7, 904 $[M_2\text{-}H+Na]^+$	3120 (NH) 2239 (CN) 1724 (C=O)	60

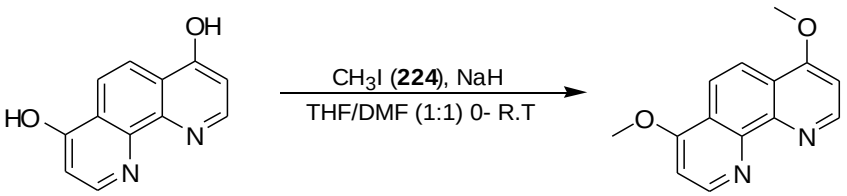
Table 41: Preparation of 4-substituted-1,2-bis[(2,2-di-methyl-4,6-dioxo-1,3-dioxan-5-ylidenemethyl)-amino]-benzene

Presence of the final products was obtained by LC-MS analysis. For example, phenanthroline **342** showed a peak at Rt = 1.6 min *m/z* = 212 ($[M]^+$, 100%), 214 ($[M+2]^+$, 14%). Furthermore, the ^1H NMR spectrum contained characteristic proton signals at δ = 8.1, 6.3 and 7.6 for the protons of 2-, 3- and 5-positions, and lacked the characteristic NH signals at δ= 11.3 ppm observed in compound **337.** However, compound **342** proved to be insoluble in hexane, THF and MTBE, the solvents required

for the borylation reaction. To help address this issue, and to test a possible strategy attachment to a solid support, the alkylation of 4,7-di-hydroxy-[1,10]-phenanthroline **342** was explored.

5.1.1.1 Alkylation of 4,7-di-hydroxy-[1,10]-phenanthroline

A review of the literature revealed that **343** can be prepared by reaction of 4,7-di-hydroxy-[1,10]-phenanthroline **342** with methyl iodide **224** using NaH in THF/DMF at room temperature (**Scheme 81**).[113]

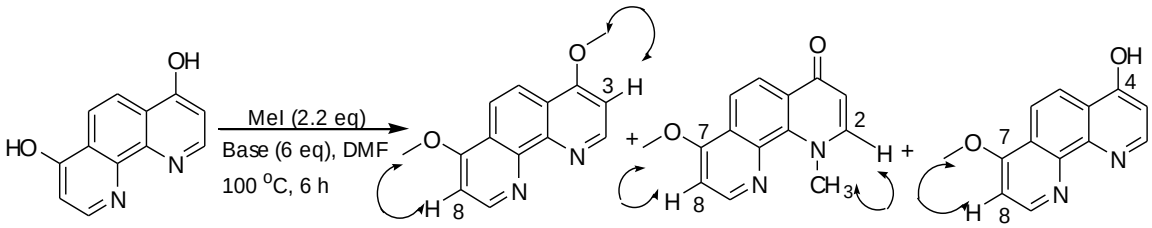


342 **343 (70%)**

Scheme 81: Di-alkylation of 4,7-di-hydroxy-[1,10]-phenanthroline[113]

However, these conditions afforded a mixture of mono- and di-alkylated products (**entry 1**, **Table 42**), as revealed by LC-MS analysis (Rt = 1.9, 2.6 and 2.0 min with *m/z* = 240 ($[M]^+$, 100%), 241 ($[MH]^+$, 48%) for **343;** *m/z* = 240 ($[M]^+$, 61%), 241 ($[MH]^+$, 100%) for **344;** 227 ($[MH]^+$, 100%) for **345**. The difference between this outcome and that reported in the literature is not obvious.[113] Following separation by chromatography, the ^{1}H NMR spectra of the obtained compounds were analysed. Product **343** contained only 4 signals, including characteristic OCH_3 signals at δ = 4.1 ppm. Alkylation at 4-C-OH and 7-C-OH was confirmed by a NOESY correlation between the OCH_3 protons with 3-H and 8-H. In contrast, product **344**[114] contained two characteristic CH_3 signals at δ = 4.1

and 4.6 ppm corresponding to alkylation at the 7-C-OH and 1-N positions, respectively. Again, this was confirmed through the NOESY spectrum which showed correlation between CH_3 protons with 2-H and 8-H. The mono-alkylated product **345** could not be isolated in a pure form. However, using only 1.0 equivalent of MeI enabled **345** to be isolated in a low yield **(26%)**. Attempts to enhance the ratio of the desired product **343** using potassium carbonate or cesium carbonate as a base with heating at 100 ^{o}C were not successful (**Table 42, entries 2&3**).



342 **343 (10%)** **344 (8%)** **345**

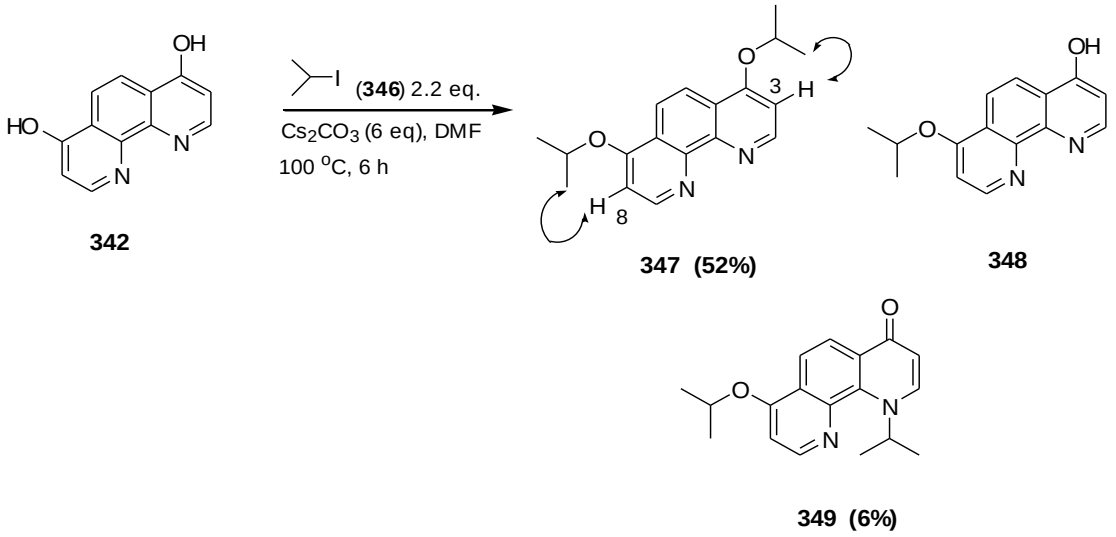
entry	Base	eq.	Solvent	T ^{o}C	time (h)	ratio[a] (343:344:345)
1	NaH	2.2	DMF:THF	r.t	18	2.0:2.8:1.0
2	K_2CO_3	6.0	DMF	100	6	1.0:5.3:---
3	Cs_2CO_3	6.0	DMF	100	6	1.0:9.0:----

[a]ratio determined by ^{1}H NMR

Table 42: Attempted di-alkylation of compound 342 using different bases

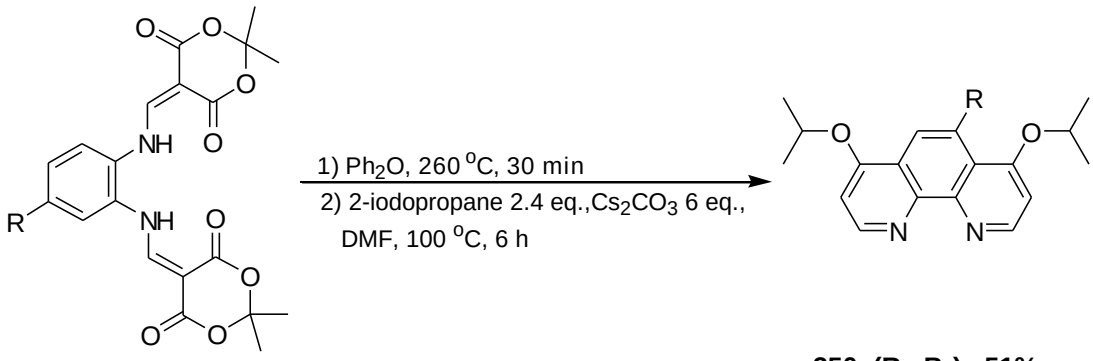
With a bis-alkoxy phen ligand in hand, it was of interest to compare the activity of ligand **343** with that of the well-established tmphen **66** in the borylation reaction. However ligand **343** proved to be insoluble in the solvents required in the borylation reactions (THF, MTBE and hexanes). Assuming that this insolubility related to π-stacking, it was decided to explore alkylation with steric larger alkyl halides such as 2-iodopropane **346,** which could be disrupt such interactions. Following the same procedure as **Table 42**, 2-iodopropane **346** and 4,7-di-hydroxy-[1,10]-phenanthroline

342 were heated at 100 °C for 6 h using cesium carbonate as base (**Scheme 82**). LC-MS analysis of the reaction mixture revealed a 97% conversion of starting material **342**, with the observation of new peaks at Rt = 2.9, 2.8 and 3.5 min with *m/z* = 296 ($[M]^+$) for **347;** *m/z* = 255 ($[MH]^+$) for **348;** *m/z* = 296 ($[M]^+$) for **349.** This indicated that the crude mixture possibly contained two isomeric di-alkylation products **347** and **349** with mono-alkylation product **348** in a ratio 77:10:10 respectively.



Scheme 82: Preparation of di-isopropoxyphenanthroline 347

Following reversed-phase chromatography (silica C18), a 52% yield of product **347** and 6% yield of product **349** were achieved. Confirmation of the proposed structures was obtained in a similar fashion to that described above. In particular for the symmetrical di-ether **347**, alkylation at 4-and 7 was confirmed by a NOESY correlation between the CH_3 signal of the isopropyl group and the protons at 3- and 8-positions. A similar sequence was used to prepare 5 substituted analogues **350** and **351** (**Scheme 83**).



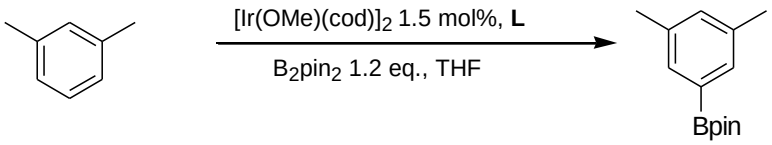
340 (R= Br)
341 (R= CN)

350 (R= Br) 51%
351 (R= CN) 65%

Scheme 83: Preparation of 5-substituted-4,7-di-isopropoxy-[1,10]-phenanthroline

5.1.2 Evaluation of Ligand 347 in the borylation of m-xylene

Following the chemistry applied (**Chapter 3, Section 3.2.2, Table 33**), ligands **347** and tmphen **66** were used as ligands in the borylation of m-xylene **19** (**Table 43**).



19 **23**

entry No	Ligand (L)	T °C	conv (%)[a] 2 h	4 h	6 h	24 h	72 h	168 h
1	347	r.t	----	----	----	----	5	23
2	66	r.t	----	----	----	5	20	49
3	347	80	58	78	82	----	----	----
4[b]	347	80	76	89	90	----	----	----
5	66	80	83	93	95	----	----	----

[a]conversion determined by ^{1}H NMR; [b][Ir(OMe)(cod)]$_2$, L (347) and B_2pin_2 were heated for 5 min at 80 °C before adding starting material

Table 43: Borylation of m-xylene using ligands 347 and 66

These reactions were followed by ^{1}H NMR spectroscopy at both room temperature and 80 ^{o}C using undecane as a standard. Attempted reactions with ligand **347** at room temperature were not efficient, but at elevated temperatures (80 ^{o}C) ligand **347** showed comparable activity to tmphen **66**. When the ligand, precatalyst and B_2pin_2 where heated together at 80˚C prior to addition of substrates (**entry 4**) the intial rates were faster suggesting that generation of the active iridium catalyst required heating. This is potentially due to the poorer solubility of these ligands. Having demonstrated that alkoxy substituted phenanthroline **347** was an active catalysts, the next objective was to attach this ligand, *via* a suitable linker, to a polymeric support.

5.1.3 Preparation of suitable linker for attachment to a polymer

5.1.3.1 Formation of C-C chain as suitable linker

Based on the report by Jones,[74] we initially explored the use of SBA-15 as a polymer supports, as these do not have C-H bonds to interfere in the borylation reaction. Of the various forms of silica support commercially accessible, MCM-41 was selected as a suitable model. MCM-41 is commercially available, whereas SBA-15 requires separate synthesis. From analysis of the desired phenanthroline polymer **356**, it was initially proposed that coupling to the polymeric support **356** could be carried out through generation of the amide from ester **355.** Compound **355** could be obtained through coupling of bromo-[1,10]-phenanthroline **350** with phenylboronate ester **354,** through a Suzuki-Miyaura cross-coupling reaction (**Figure 34**). With this plan, the initial goal was the preparation of ester **354** which is discussed in the next section.

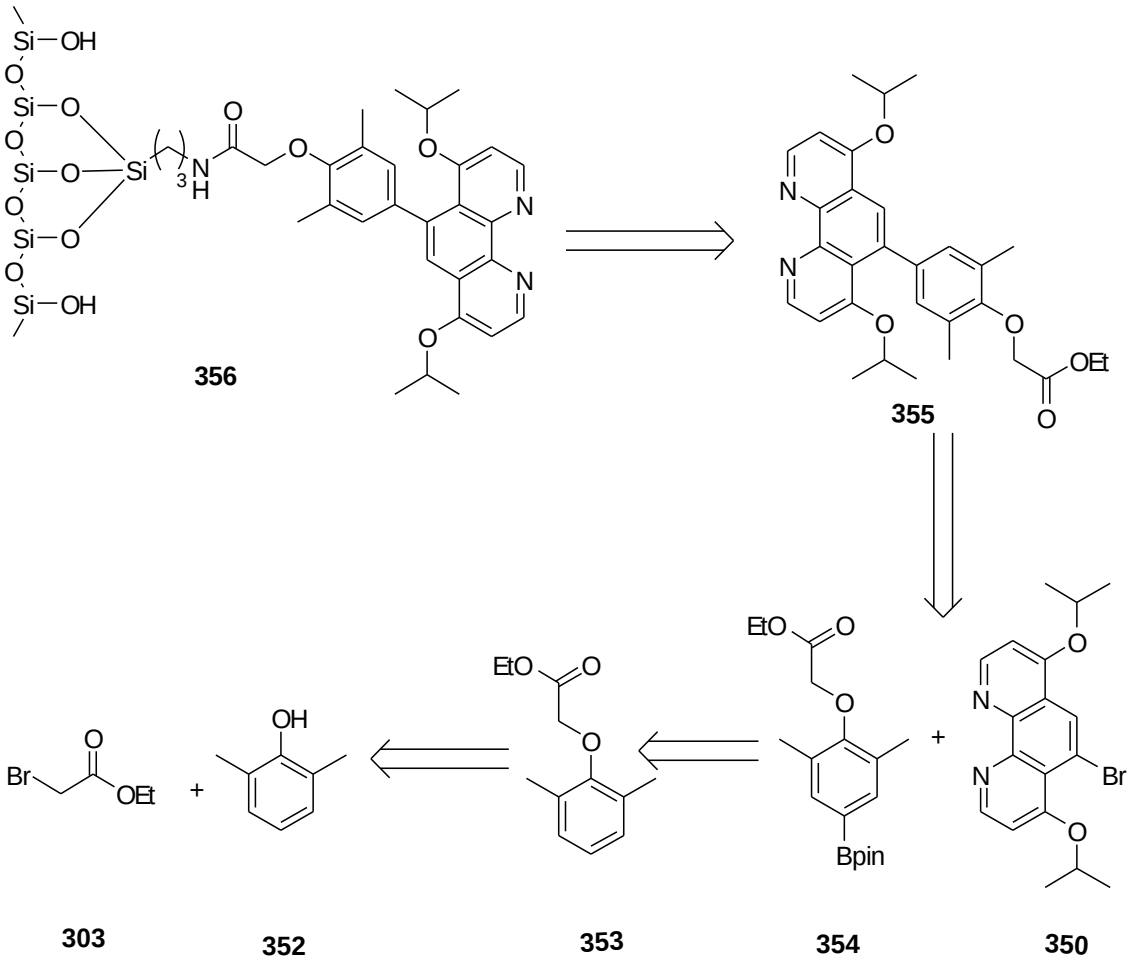
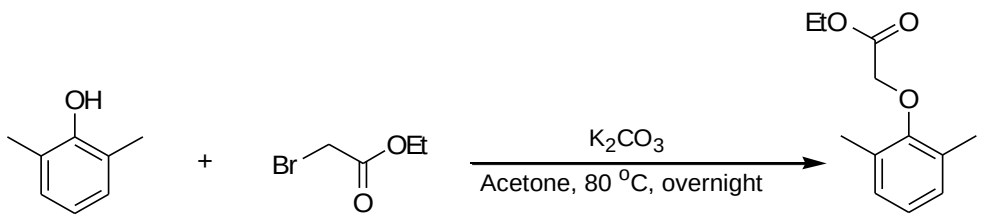


Figure 34: Strategy for immobilisation of [1,10]-phenanthroline ligands

5.1.3.1.1 Borylation of (2,6-di-methyl-phenoxy)-acetic acid ethyl ester 353

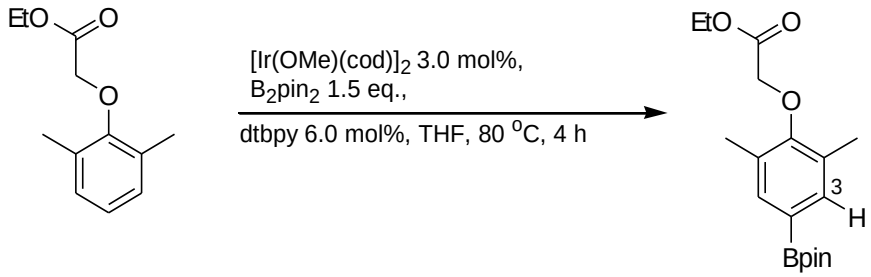
It was planned that aryl boronate ester **354** could be obtained through the alkylation of 2,6-di-methylphenol **352** with ethylbromoacetate **303**, followed by borylation of the resulting (2,6-di-methyl-phenoxy)-acetic acid ethyl ester **353**. Ester **353** was prepared in good yield (96%) through heating of 2,6-di-methylphenol **352** with ethyl bromoacetate **303** in the presence of K_2CO_3 in acetone at 80 ^oC (**Scheme 84**).



352 **303** **353 (96%)**

Scheme 84: Preparation of (2,6-di-methyl-phenoxy)-acetic acid ethyl ester

Confirmation of the proposed structure was obtained by the ^{1}H NMR spectrum which showed a shift in the CH_2 signal from 3.8 ppm ($BrCH_2$) to 4.4 ppm ($ArOCH_2$). Borylation using $[Ir(OMe)cod]_2$ **21**, dtbpy **22** and B_2pin_2 in THF proved to be efficient affording **354** in 56% yield, following chromatography.

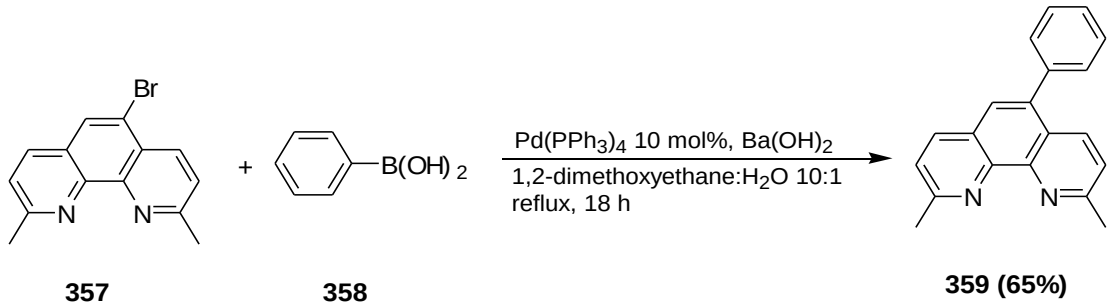


353 **354 (56%)**

Scheme 85: Borylation of (2,6-di-methyl-phenoxy)-acetic acid ethyl ester 353

This product was confirmed by the ^{1}H NMR spectrum analysis, which showed a complex methyl signal multiplet integrating to 15H at δ = 1.35-1.25 ppm for both Bpin moiety and CH_3 of the ester. Moreover the 3-H signal shows the characteristic shift downfield from δ = 7.0 to δ = 7.5, due to the inductive effect caused by the *ortho* Bpin group. Having successfully generated the arylboronate ester **354,** it was necessary to

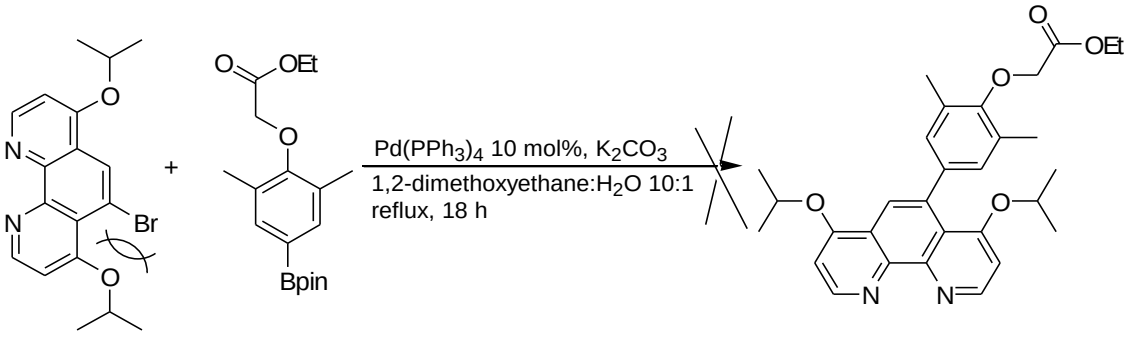
attach the ligand **347** to a polymer. As described above, initial attempts explored Suzuki-Miyaura cross-coupling reactions. A survey of recent methods[115] revealed that similar compounds have been prepared by the coupling of 5-bromo-2,9-di-methyl-[1,10]-phenanthroline **357** with phenylboronic acid **358** using $Pd(PPh_3)_4$ and $Ba(OH)_2$ in a 10:1 mixture of 1,2-di-methoxyethane:water (**Scheme 86**).



357 **358** **359 (65%)**

Scheme 86: Preparation of 5-phenyl-2,9-di-methyl-[1,10]-phenanthroline[115]

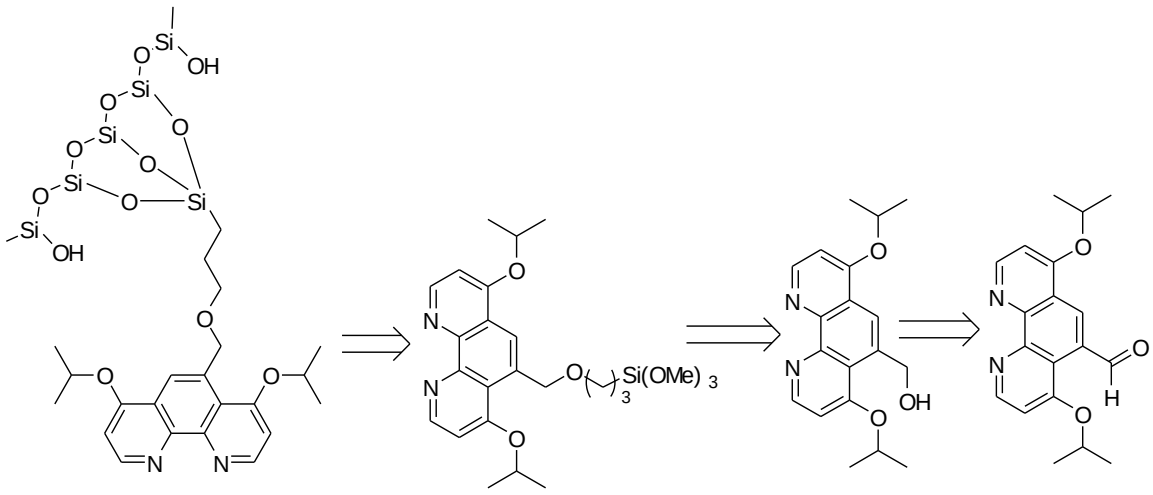
Despite this precedent, coupling of bromophenanthroline **350** with arylboronate ester **354** following these conditions was unsuccessful. Attempts to vary the base, such as Cs_2CO_3 and K_3PO_4, and changing the catalyst to $PdCl_2$(dppf) proved equally unsuccessful (**Scheme 87**). Control experiments using both unsubstituted phenylboronic acid and potassium phenyltri-fluoroborate also failed. It was speculated that either the steric bulk of the 4-isopropoxy group or coordination of Pd to the phenanthroline nitrogen's inhibited any catalytic activity.



350 **354** **355**

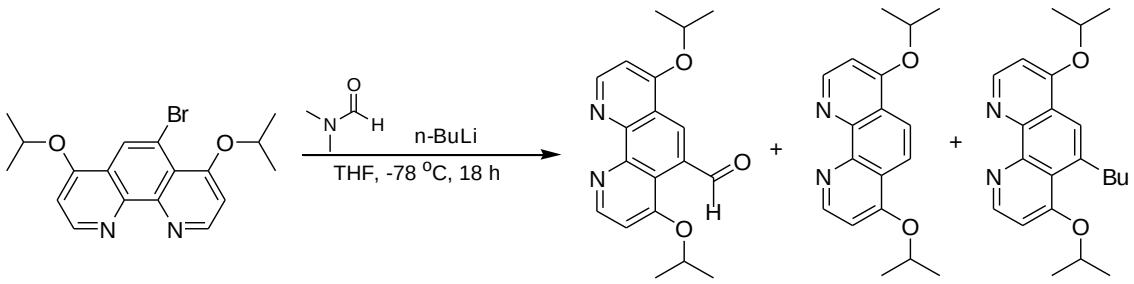
Scheme 87: Preparation of 5-aryl-4,7-di-ispropoxy-[1,10]-phenanthroline

In an alternative pathway, a hydroxmethyl group at the 5-position of the phenanthroline ring **361**, was proposed to enable introduction of tri-methoxysilane **362** by simple alkylation (**Figure 35**). Compound **360** was obtained by lithiation of 4,7-di-isopropoxy-5-bromo-[1,10]-phenanthroline **350** using n-BuLi in THF, followed by the addition of dry DMF[116] at -78 ^{o}C (**Scheme 88**).



363 **362** **361** **360**

Figure 35: Retrosynthetic analysis of grafting tri-methoxysilane onto MCM-41

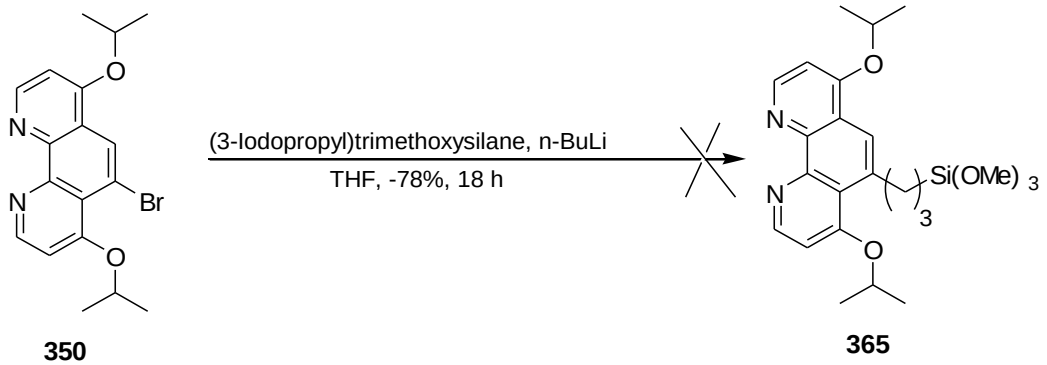


350 **360** **347** **364**

Conv. (%)	LC-MS ratio (360:347:364)
100	37:49:14

Scheme 88: Preparation of 4,7-di-isopropoxy-[1,10]-phenanthroline-5-carbaldehyde

Although this reaction proceeded with complete consumption of the starting material **350**, only small amounts of the desired aldehyde **360** and two undesired products **347** and **364** were obtained. Attempts to produce tri-methoxysilane **365** directly through anion alkylation, (**Scheme 89**) were similarly unsuccessful.

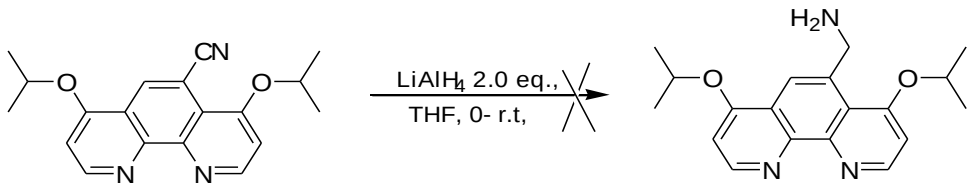


350 **365**

Scheme 89: Preparation of 4,7-di-isopropoxy-1,10-phenanthrolin-5-yl-propyltri-methoxysilane

Recognising that a similar aminomethyl linker **366** could be generated from nitrile reduction, the reduction of 4,7-di-isopropoxy-5-cyano-[1,10]-phenanthroline **351** was

then explored. However this could not be achieved using $LiAlH_4$[117] in THF or Pd/C[118] with H_2 (**Scheme 90**).



351 **366**

Scheme 90: Preparation of 4,7-di-isopropoxy-[1,10]-phenanthrolin-5-yl-methylamine

From these attempts, it became clear that the formation of a C-C chain on the 5-position of phenanthroline derivatives **332** (**Figure 32**) was challenging. Consequently, an alternative pathway to the desired material was sought. It was proposed that the formation of a O-C chain at the 4-position of the phenanthroline **333** (**Figure 32**) could function as a suitable linker to a polymer. In order to form a O-C bond, mono-alkylation of 4,7-di-hydroxy-[1,10]-phenanthroline **342** was required. This is discussed in the next section.

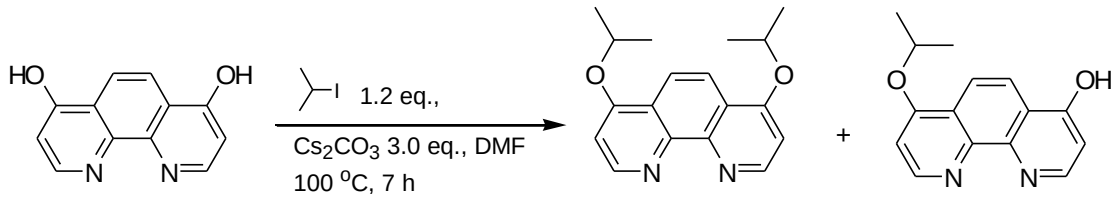
5.1.3.2 Formation of O-C chain as a suitable linker

With the failure to develop a linker based on the 5- functionalised di-isopropyl ligands (**361 & 366),** attention turned to coupling to the polymer through one of the alkoxy substituents. Three strategies were envisaged to enable coupling of phenanthroline **348** to an MCM-41 support. The first approach involved combining tri-methoxysilane with ligand **367**, then grafting this to the polymer (**Figure 36**). The second approach involved building of a suitable linker on a polymer before adding the phenanthroline **348 (Scheme 114**). The final possibility involved attaching linker elements to both

components **368** and **369,** which are then combined in a final step (**Figure 38**). Each of these strategies required the preparation of monoalkoxyphenanthroline **348** described in the following section.

5.1.3.2.1 Preparation of 4-hydroxy-7-isopropoxy-[1,10]-phenanthroline

As discussed above a key intermediate for immobilisation of the phen ligand was the monoalkoxy ether **348**. This had previously been identified as a minor by-product from the preparation of di-alkoxy ether **347** (**Section 5.1.1.1, Scheme 82).** In order to generate the desired monoether **348** selectively, the reaction stoichiometry was investigated. Ultimately, heating 1.2 eq. 2-iodopropane with 4,7-di-hydroxy-[1,10]-phenanthroline **342** at 100 ^{o}C for 7 h (**Scheme 91**) afforded a mixture of mono- and di-alkylation in a ratio 1:4 of compounds **347** and **348**, as observed by ^{1}H NMR spectroscopy.



342 **347** **348 (45%)**

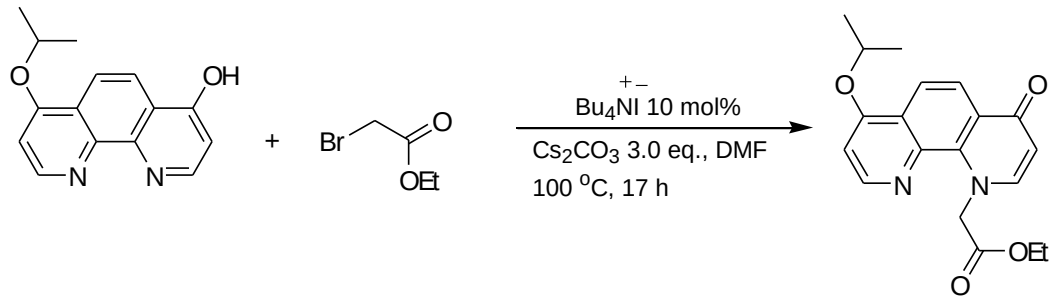
^{1}H NMR ratio (347:348)

1.0:4.0

Scheme 91: Preparation of 4-hydroxy-7-isopropoxy-[1,10]-phenanthroline

Following extraction of the desired product **348** by 10% NaOH (aq.), a 45% yield of monoalkylated product **348** was obtained without the need for further purification.

Attempts to increase the proportion of mono to di-alkylation-phenantholine through controlling the rate of addition of the alkylating agent to the phenoxide anion gave surprising results. It was observed that adding the alkyl halide rapidly to the reaction mixture at 100 ^{o}C gave enhanced levels of monoalkyaltion whilst slow addition afforded a ~1:1 mixture of mono to bis-alkylated products. An explanation for this is not obvious. However this approach did allow reliable access to the desired phenanthroline building block **348**. With ligand **348** in hand, the next objective was the preparation of a suitable linker to allow attachment to a polymer. The first approach involved heating mono-alkoxy-[1,10]-phenanthroline **348** with ethyl bromoacetate **303** in DMF at 100 ^{o}C for 17 h in presence of cesium carbonate and tri-butylammonium iodide (**Scheme 92**).

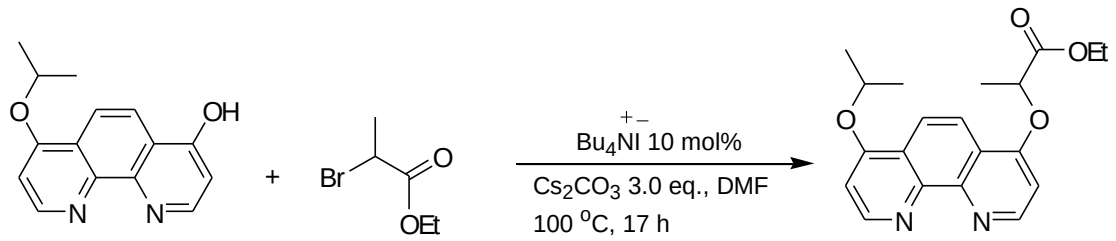


348 **303** **370 (21%)**

Scheme 92: Alkylation of phenanthroline 348 with ethyl bromoacetate

However, this afforded the undesired N-alkylated product **370** as confirmed through an observed NOESY correlation between the *N*-CH_2 and 2-H signals. Further evidence was obtained from the IR spectrum which showed two carbonyl peaks at 1739 cm^{-1} and 1623 cm^{-1} due to the stretching vibration of (C=O) ester and vinylogous amide bonds respectively. This undesired alkylation was observed in previous attempts using

methyl iodide.[114] In this case the desired O-alkylation was achieved using 2-iodopropane.[113] Consequently, it was speculated that similar selectivity could be achieved using ethyl-2-bromopropanoate **371** instead of ethyl bromoacetate **303**. Pleasingly this proved to be the case, affording the desired ether **367** as evidenced from LC-MS analysis which revealed a peak at Rt = 2.6 min with *m/z* = 354 ($[M]^+$, 100), 731 ($[M_2Na]^+$) with alkylation at 4-C-O-CH(CH_3) being confirmed by a NOESY correlation between the alpha ester hydrogen ($OCHCO_2Et$) and 3-H (**Scheme 93**).

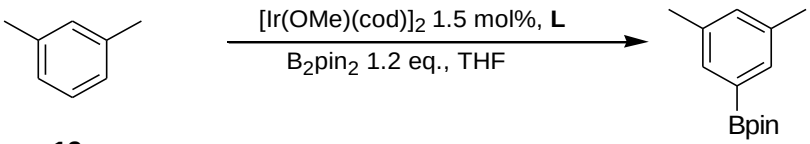


348 **371** **367 (66%)**

Scheme 93: Preparation of 2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-propionic acid ethyl ester

5.1.4 Evaluation of Ligand 367 in the borylation of m-xylene

At this stage it was of interest to evaluate the efficacy of ligand **367** in the borylation reaction. Following the same procedure used previously (**Section 5.1.2**), the activity of ligand **367** was compared to that obtained using ligand **347**. Importantly and, as expected, the two ligands showed comparable activity (**Table 44**).



19 **23**

entry No	Ligand (L)	temp. °C	conv (%)[a] 2 h	4 h	6 h	24 h	72 h	168 h
1	347	r.t	----	----	----	----	5	23
2	367	r.t	----	----	----	9	13	18
3	347	80	58	78	82	----	----	----
4[b]	347	80	76	89	90	----	----	----
5[b]	367	80	77	89	91	----	----	----
6[b]	367	80	75	90	92	----	----	----
7	367	80	63	88	92	----	----	----

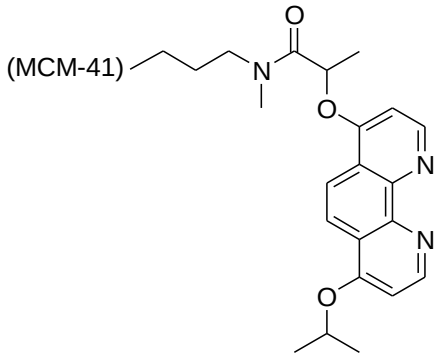
[a] conversion determined by ^{1}H NMR; [b][Ir(OMe)(cod)]$_2$, L and B_2pin_2 were heated for 5 min at 80 °C before adding starting material

Table 44: Evaluation of ligand 367 in the borylation of m-xylene

5.1.5 Attempted generation of MCM-41 supported Ligands

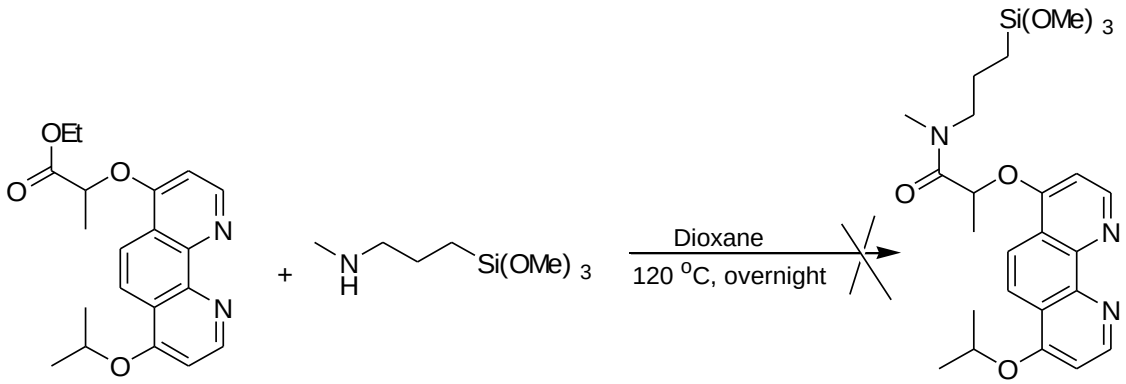
Because of the difficulty in characterisation of the desired heterogeneous phenanthroline-MCM-41 **372** (**Figure 36**), it was decided to attach the linker to the ligand and only then couple to the polymer support. As a result the first approach was to explore amide derivatives. This could simply be achieved by heating phenanthroline ester **367** with amine-tri-methoxysiliane **373** (**Scheme 94**). Disappointingly this reaction was unsuccessful even when using prolonged reaction times with base or acid catalysis[119]. With this, it was proposed that introducing an alkyne tail to the phen ligand would enable coupling to a polymeric azide **375** (**Figure 37**). The former could be obtained through the alkylation of alkoxyphenanthroline **348** with 2-bromo-*N*-(prop-2-

yn-1-yl) propanamide **378**. With this in mind preparation of propanamide **378** became the initial objective. This was prepared through facile reaction of 2-bromo-propionyl chloride **376** and propargylamine **377** (1.0 eq.) using Et_3N in DCM at 0 ^oC (**Scheme 95**)



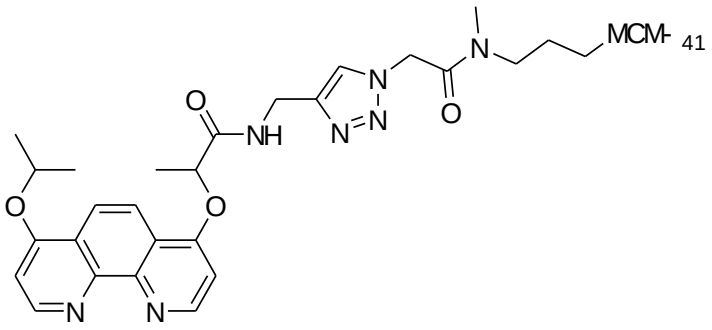
372

Figure 36: Heterogeneous phenanthroline-MCM-41 (372)



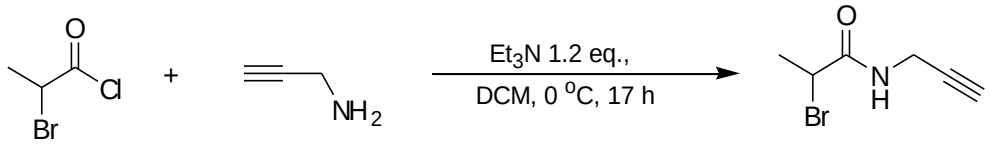
367 **373** **374**

Scheme 94: Preparation of amide 374 through coupling ester 367 with amine



375

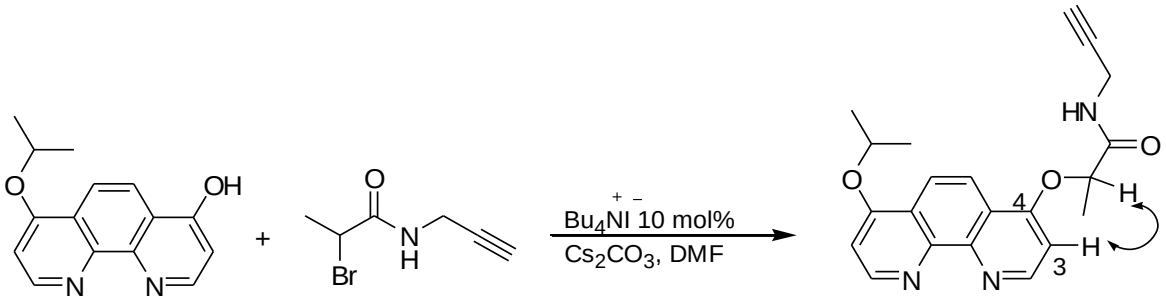
Figure 37: MCM-41 supported ligand using triazole as linker



376 **377** **378 (88%)**

Scheme 95: Preparation of 2-bromo-*N*-(prop-2-yn-1-yl)-propanamide 378

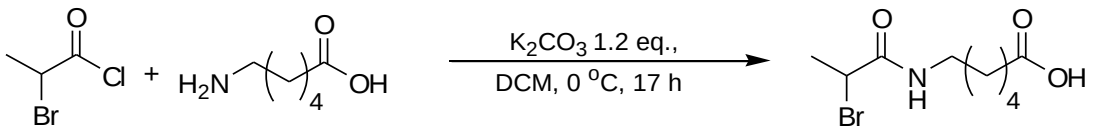
Product **378** was isolated in 88% yield. The proposed structure of this product was confirmed by ^{1}H NMR, which showed a shift in the CH_2 signal from 3.5 ppm (NH_2CH_2) to 4.05-3.94 ppm ($NHCH_2$). With compound **378** in hand, alkylation of 4-hydroxy phenanthroline **350** was then attempted (**Scheme 96**).



348 **378** **379 (17%)**

Scheme 96: Preparation of 2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-*N*-prop-2-ynyl-propionamide 379

Following chromatography, the desired ether **379** was obtained, as characterised by a molecular ion at *m/z* = 364 and a distinctive NOESY correlation between the methane signal and the 3-H of the phen ligand (depicted in **Scheme 96**). Disappointingly the isolated yield was poor, and despite variations in the conditions above could not be further improved. Given this result, alternative modes to connect the two fragments based on an amide coupling were considered. In this approach the initial strategy involved the amide linker being assembled, coupled to the ligand and, subsequently, the polymeric support. This required access to 6-(2-bromo-propionylamino)-hexanoic acid **381** which could be generated through the reaction of 2-bromopropionyl chloride **376** with 6-amino caproic acid **380** in presence of K_2CO_3 in DCM at 0 ^oC for 17 h (**Scheme 97**).

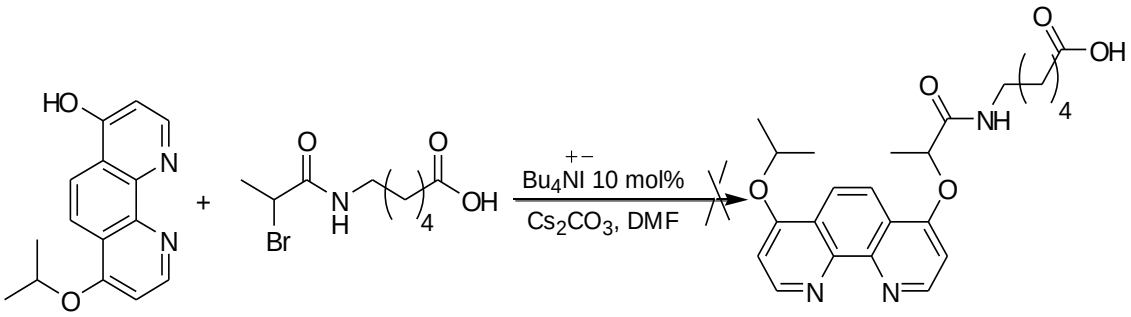


376 **380** **381 (43%)**

Scheme 97: Preparation of amide 381

Analysis by LC-MS showed complete conversion of carboxylic acid **380**, indicating that the crude mixture contained the desired product **381**. A 43% yield of the desired product **381** was obtained following acidification of aqueous solution (pH=2-3), with subsequent trituration from di-ethylether. Formation of amide **381** was confirmed the appearance of a peak in the LCMS spectrum at Rt = 2.2 min with *m/z* = 266 ([M (^{81}Br)-H]$^-$, 100%), 264 ([M (^{79}Br)-H]$^-$, 100%) coupled with IR spectrum analysis, which revealed

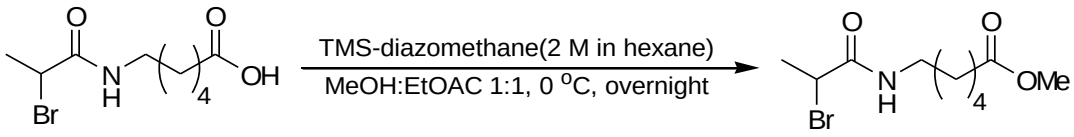
two absorptions at 1700 cm^{-1} and 1652 cm^{-1} due to the C=O stretching vibrations of the acid and amide bonds respectively. Disappointingly, attempted alkylation of 4-hydroxyphenanthroline **350** with 6-(2-bromo-propionylamino)-hexanoic acid **381** (1 eq.) following the same protocol as described above, did not give the desired product **382** (**Scheme 98**).



348 **381** **382**

Scheme 98: Preparation of 6-[2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-propionylamino]-hexanoic 382

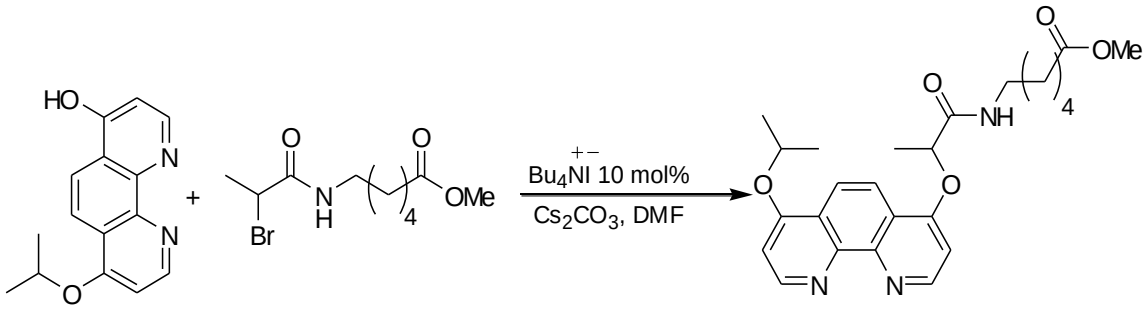
Assuming that the free carboxylic acid was interfering with the coupling, the corresponding methyl ester **383** was prepared using TMS-diazomethane[120] in MeOH:EtOAc 1:1 at r.t overnight (**Scheme 99**).



381 **383 (89%)**

Scheme 99: Preparation of 6-(2-bromo-propionylamino)-hexanoic acid methyl ester 383

Ester **383** was obtained in 89% isolated yield and characterised by ^{1}H NMR analysis which showed a characteristic methyl signal for the ester group at δ = 3.5 (3H,s, OMe). Furthermore, a peak at 1734 cm^{-1} was observed in the IR spectrum, due to the stretching vibration of (C=O) ester bonds. With the ester **383**, the alkylation proceeded efficiently to afford complete conversion of phenanthroline **348** as determined by LCMS (Rt = 2.5 *m/z* = 930 ([M_2H]$^+$, 30%), 454 ([MH]$^+$, 100%)) (**Scheme 100**).



348 **383** **384**

Scheme 100: Preparation of 6-[2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-propionylamino]-hexanoic acid methyl ester 384

Unfortunately, all attempts to purify this compound were unsuccessful and, given the difficulties in assembling this linker, alternative modes of coupling to the polymer were investigated. With the unsuccessful attempt to couple the caproate to the phen ligand it was decided to explore building the linker onto the polymeric support and forming the key amide bond as the final step. Grafting *N*-methylaminopropyltri-methoxysilane onto MCM-41 therefore became the first objective

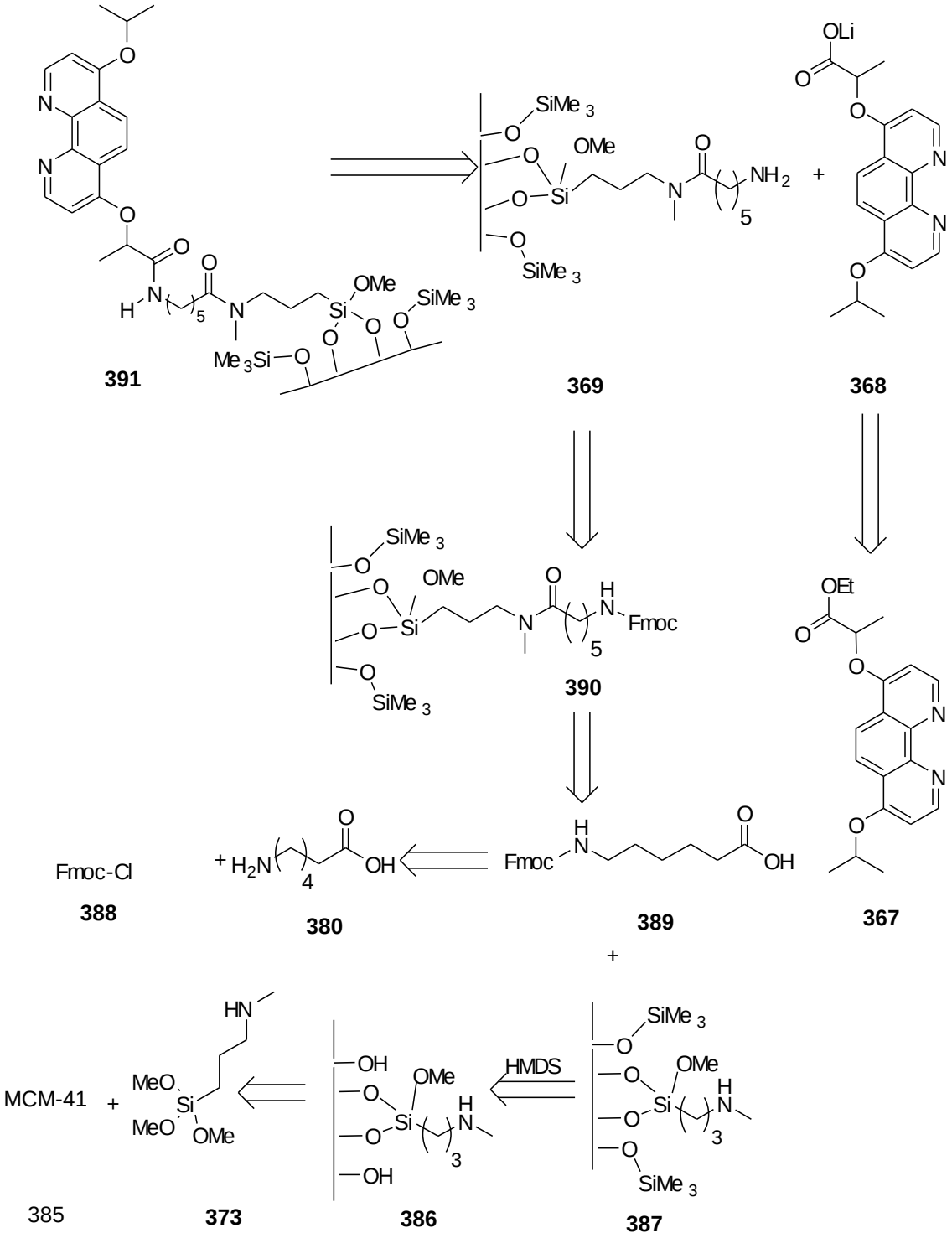
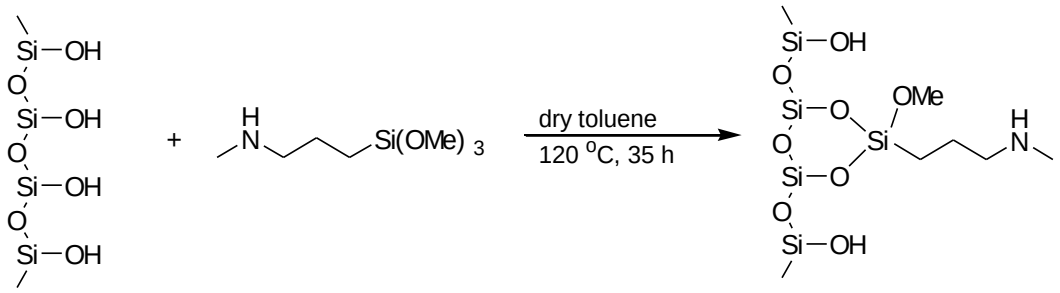


Figure 38: Retrosynthetic of the desired polymer 391

5.1.5.1 Grafting N-methylaminopropyltri-ethoxysilane 374 onto (MCM-41) 385

Following literature protocols,[121-124] *N*-methylaminopropyltri-methoxysilane **373** was mixed with (MCM-41) **385** in dry toluene. The reaction mixture was then heated to reflux at 120 ^{o}C for 35 h (**Scheme 101**).



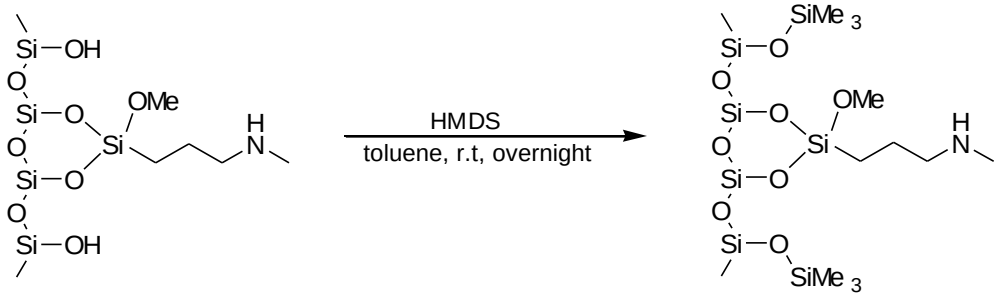
385 **373** **386**

Scheme 101: Grafting the *N*-methylaminopropyl-tri-ethoxysilane 374 onto (MCM-41) 385

Following washing with dry toluene and methanol, the desired aminofunctionalised polymer **386** was obtained (1.21 mmol/g polymer). The proposed compound was characterised by elemental analysis (**CHN found C% 10.58, H% 2.69, N% 7.74; $C_5H_{13}NOSi$ required C% 45.76, H% 9.98, N% 10.67**) and ^{13}C NMR solid state spectroscopy, revealing characteristic methyl signals at δ = 50 for the MeOSi and NCH_2 groups, which confirmed that only one methoxy group remained after grafting the trimethoxysilyl **373** onto MCM-41.

5.1.5.2 End-Capping the functionalized MCM-41

Because the residual hydroxyl groups on the MCM-41 polymer may interfere with subsequent reaction, these were then capped as silyl ethers. This was achieved by shaking the modified polymer **386** with HMDS in toluene at room temperature overnight (**Scheme 102**). Further ^{13}C NMR solid state analysis showed characteristic methyl signals at $\delta = 0.0$ for the $OSi(CH_3)_3$ group.

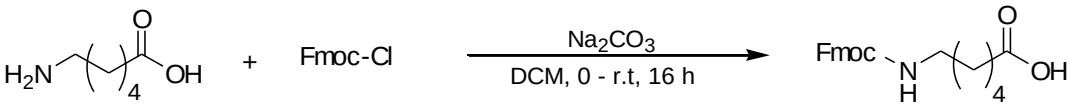


386 **387**

Scheme 102: End-Capping the functionalized (MCM-41) 387

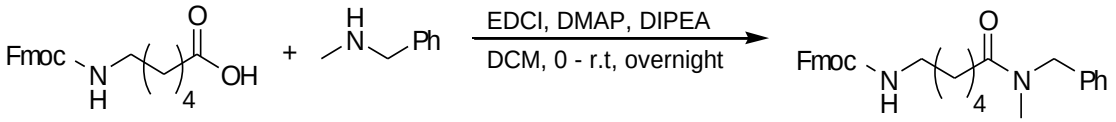
Given the difficulties in assessing loading of aminomethyl group by simple measurements, it was decided to introduce an Fmoc group to exploit classical Fmoc analysis.[125,126] This required a suitable Fmoc terminated linker. Consequently, following a reported protocol,[127] 6-(9H-fluoren-9-ylmethoxycarbonylamino)-hexanoic acid **389** was prepared by stirring of 6-amino caproic acid **380** with Fmoc-Cl **388** and Na_2CO_3 in dioxane:H_2O at r.t (**Scheme 103**). With Fmoc acid **389** in hand, coupling to the polymeric amine was then explored. Initially, a model reaction using *N*-methylbenzylamine **392** was undertaken. Using EDCI in presence of DMAP and DIPEA in DCM at r.t,[128] and following chromatography, a 27% yield of the desired amide **393** was obtained (**Scheme 104**). The proposed structure was confirmed by LC-MS analysis

which showed a peak at Rt = 3.8 min *m/z* = 936 ($[M_2H+Na]^+$, 100%), 457 ($[MH]^+$, 56%), indicating the correct mass for the desired product. Despite the low yield this positive result encouraged us to explore the coupling of sec amine-(MCM-41) **387** with Fmoc-COOH **389**. Following this precedent,[128] the desired Fmoc polymer **390** was obtained through coupling of Fmoc-COOH **389** with *N*-methylamine-(MCM-41) **387** (**Scheme 105**).



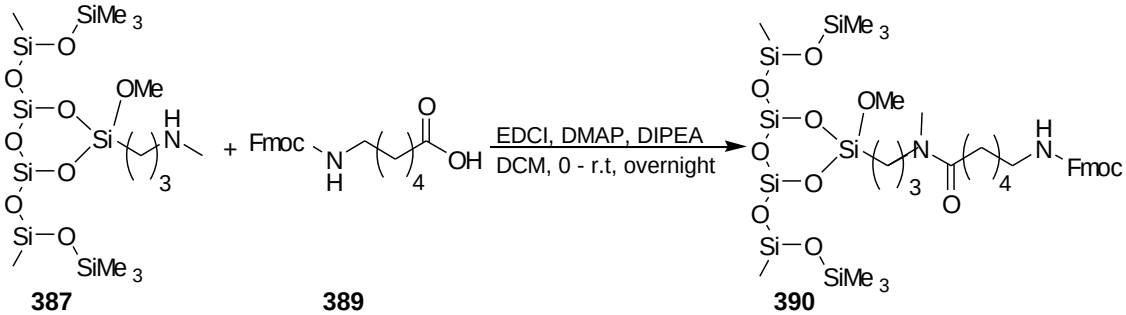
380 **388** **389 (87%)**

Scheme 103: Preparation of 6-(9H-fluoren-9-ylmethoxycarbonylamino)-hexanoic acid 389



389 **392** **393 (27%)**

Scheme 104: Preparation of 6-(9H-fluoren-9-ylmethoxycarbonylamino)-hexanoic acid 393

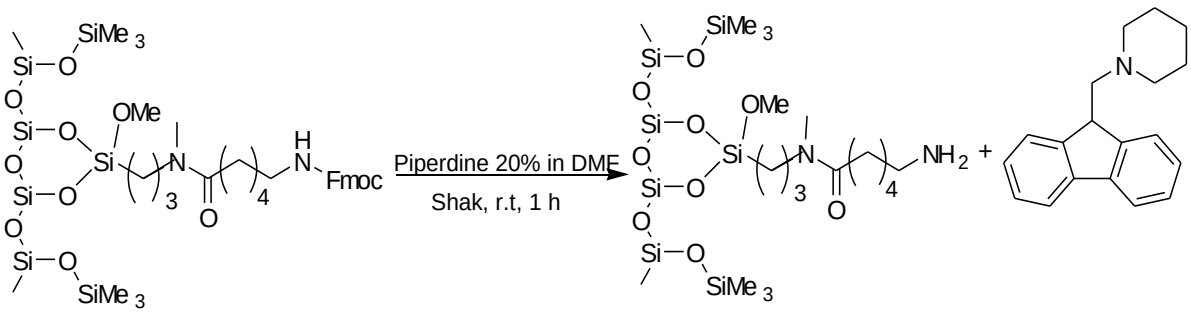


387 **389** **390**

Scheme 105: Immobilising the Fmoc onto (MCM-41) 390

In order to ensure high conversion of the polymeric amine, the reaction was repeated twice. Formation of the desired amide was confirmed by solid state ^{13}C NMR, showing

additional peaks at 40 and 27 ppm for the aliphatic groups, 125 ppm and 141 ppm for the aromatic of Fmoc ring, and 174 for the C=O amide. In addition, the IR spectrum showed a peak at 1600 cm^{-1} due to the stretching vibrations of (C=O) amide bond. Following standard literature protocols[129,130] the Fmoc group was removed using 20% piperidine in DMF (**Scheme 106**). In this reaction 1 g of **390** was divided into two portions **(X** & **Y)** and each was shaken with the same volume of 20% piperidine to remove the Fmoc (**Section 6.2.33, Table 45**). UV measurement of the solution at λ = 300 nm, followed by analysis using the Beer-Lambert law was used to determine the concentration of the piperidine fulvene adduct in both solutions (the equation of which is discussed in section **6.2.33**.[129] Disappointingly, this suggested that very low loading of the amine onto MCM-41 polymer (0.018 mmol/g) had been achieved. However it was decided to continue and explore the coupling of this amine to the Phen ligand **368**.

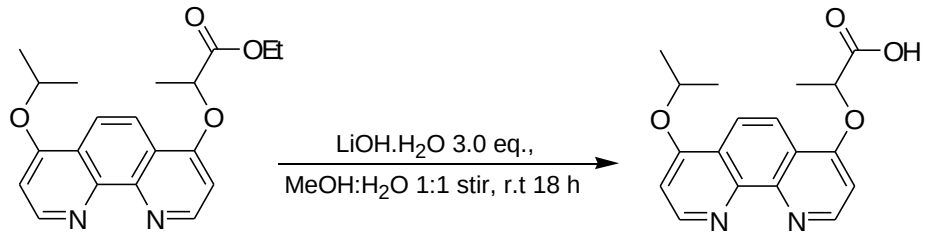


390 **369** **394**

Scheme 106: Deprotecting of amine using piperidine

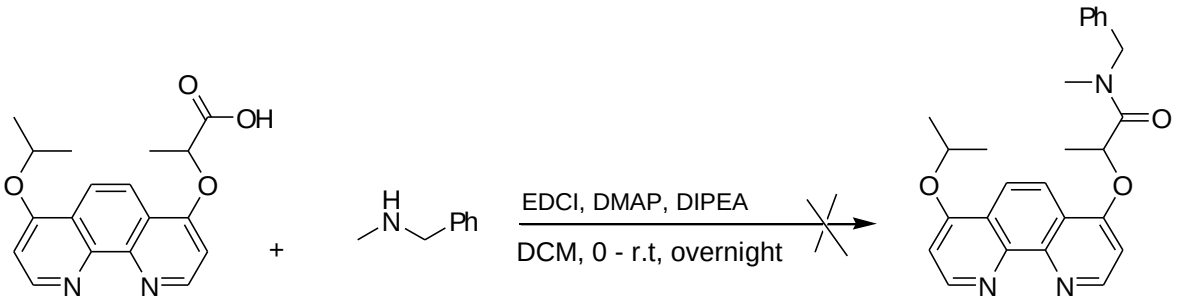
Based on the retrosynthetic analysis discussed in section **5.1.5, Figure 38**, it was proposed that the amide could be prepared by coupling of an amine such as the MCM-41 polymer **369** with either carboxylic acid or the corresponding lithium salt.[128,131] Consequently, the initial task was to hydrolyse the ester. This was achieved using LiOH

in methanol and and water with following acidification and extraction, gaving a 31% yield of 2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-propionic acid **395** (**Scheme 107**) as confirmed by LC-MS analysis which showed a peak at Rt = 2.2 min *m/z* = 651 ($[M_2\text{-}H]^-$, 100%), 325 ($[M\text{-}H]^-$, 48%). In addition, the ^1H spectrum NMR lacked the characteristic ethyl ester signals. With the acid **395** available, the first reaction undertaken was a model coupling with *N*-methylbenzylamine **392** (**Scheme 108**). However following the procedure previously used to generate amide **396** using EDCI was not successful. One possible reason for this observation could be the steric hindrance in both reagents.



367 **395 (31%)**

Scheme 107: Hydrolysis of ester using LiOH

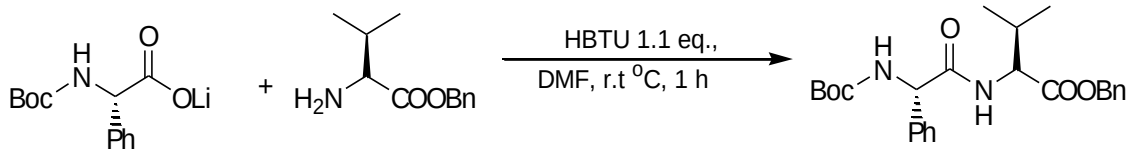


395 **392** **396**

Scheme 108: Preparation of amide using EDCI

Consequently, an alternative pathway was sought. A survey of the literature suggested that carboxylate salts provide greater reactivity in formation of sterically hindered

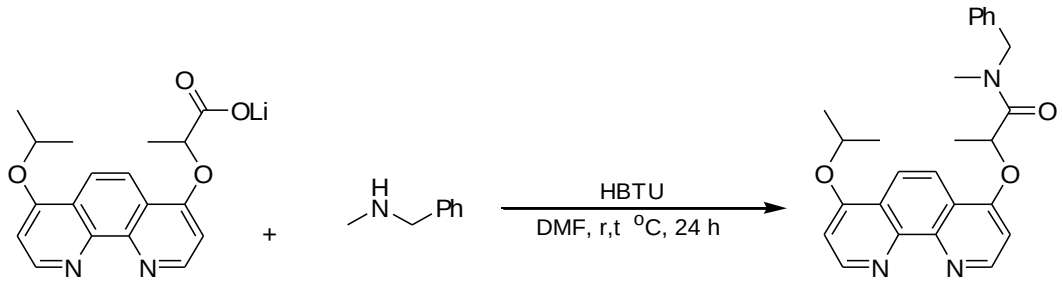
amides. For example, amide **399** can be prepared from the coupling reaction of amine **398** with lithium carboxylate **397** using HBTU in DMF (**Scheme 109**).[131]



397 (1.1 eq.) **398 (1.0 eq.)** **399 (quant yield)**

Scheme 109: Preparation of amide 399 using HBTU[131]

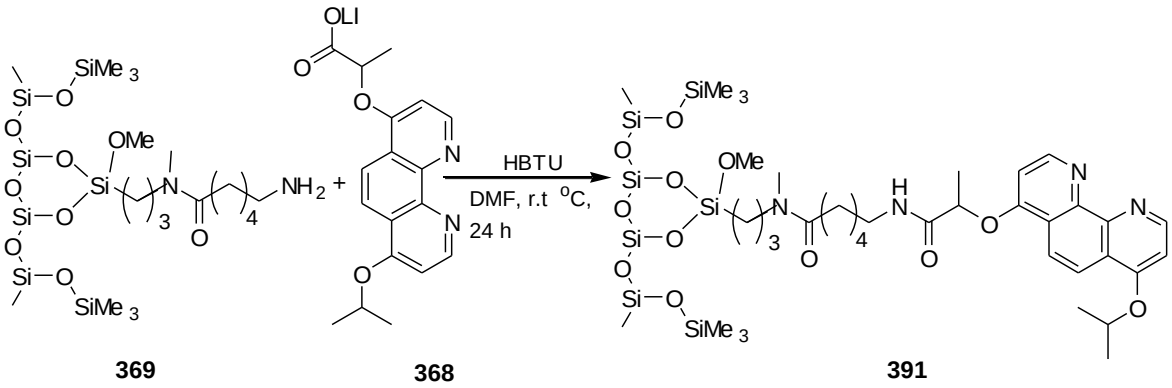
In order to follow this precedent, the preparation of the phenanthroline lithium carboxylate **368** was required. This lithium salt was accessed by hydrolysis of ester **367** prior to removal of the solvent under reduced pressure. As before, prior to using the precious polymeric amine **369**, a model study with *N*-methylbenzylamine **392** was undertaken (**Scheme 110**). Following the literature precedent[131]utilising HBTU afforded the desired amide **396**, as charcterised by a new peak at Rt = 2.9 min *m/z* = 882 ($[M_2H+Na]^+$, 18%), 430 ($[MH+]^+$, 100%) in the LC-MS trace. However, full conversion was not observed by LCMS, and following chromatography a 20% yield of the phenanthroline amide **396** was obtained.



368 **392** **396 (20%)**

Scheme 110: Preparation of *N*-benzyl-2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-*N*-methyl-propionamide 396

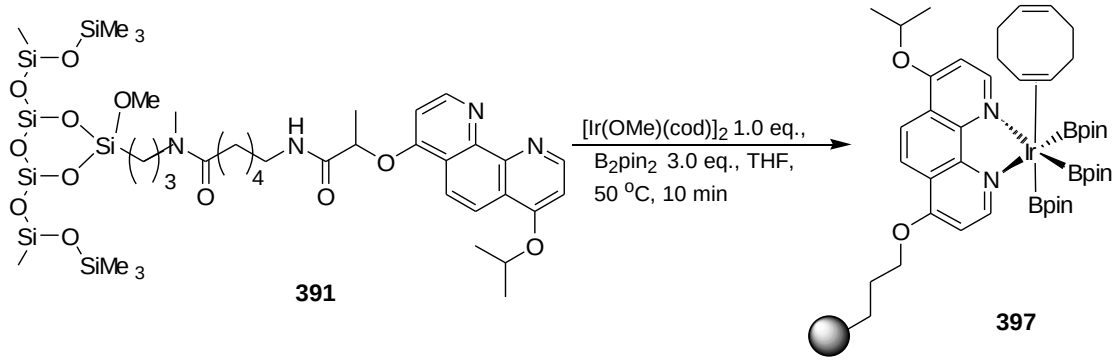
With successful formation of the desired amide bond, attention then turned to coupling of MCM-41 amine **369** with the phenanthroline lithium salt **368**. Following the same procedure, but using 3 equivalents of phenanthroline salt **368** to MCM-41 amine **369** to enhance conversion, the generation of the polymeric ligand **391** was attempted (**Scheme 111**).



369 **368** **391**

Scheme 111: Preparation of the desired polymer 391

Disappointingly, confirmation of the desired polymer using solid state NMR analysis was not possible. This may be due to the very low loading of the primary amine onto MCM-41. Consequently, in order to confirm whether the ligand had been immobilised onto MCM-41 coordination of the Ir catalyst was attempted. Following the standard procedure used to generate the tris boryliridium catalyst (**Chapter 1, Section 1.1.5**) 500 mg of polymer **391**, $[Ir(OMe)(cod)]_2$ (1 eq.) and B_2pin_2 (3 eq.) were mixed in dry degased THF (2 ml) at 50 °C for 10 min (**Scheme 112**). The polymer was then washed, under argon, with dry degased THF, dried *in vacuo* and then used directly to borylate m-xylene. This reaction was carried out at 80 °C for 6 h and, following washing with dry degased THF, the resulting solution was collected and concentrated *in vacuo*.

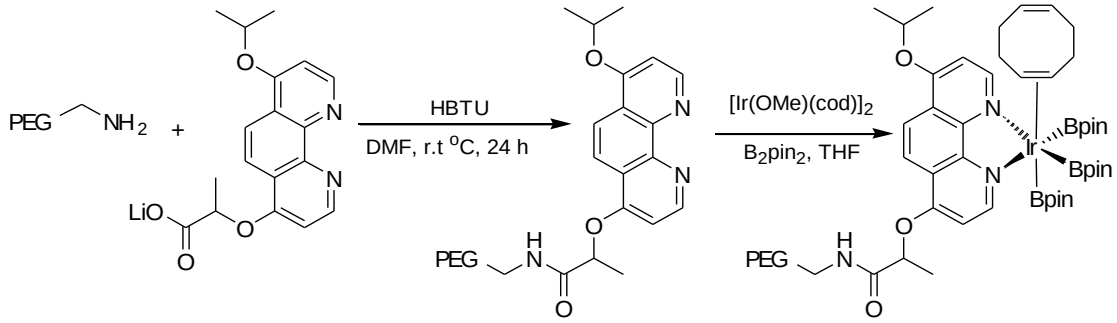


Scheme 112: Preparation silica supported iridium catalyst 399

Disappointedly, no borylated product could be detected by GC-MS analysis. This may be due to the low loading of the ligand **368** on a polymer.

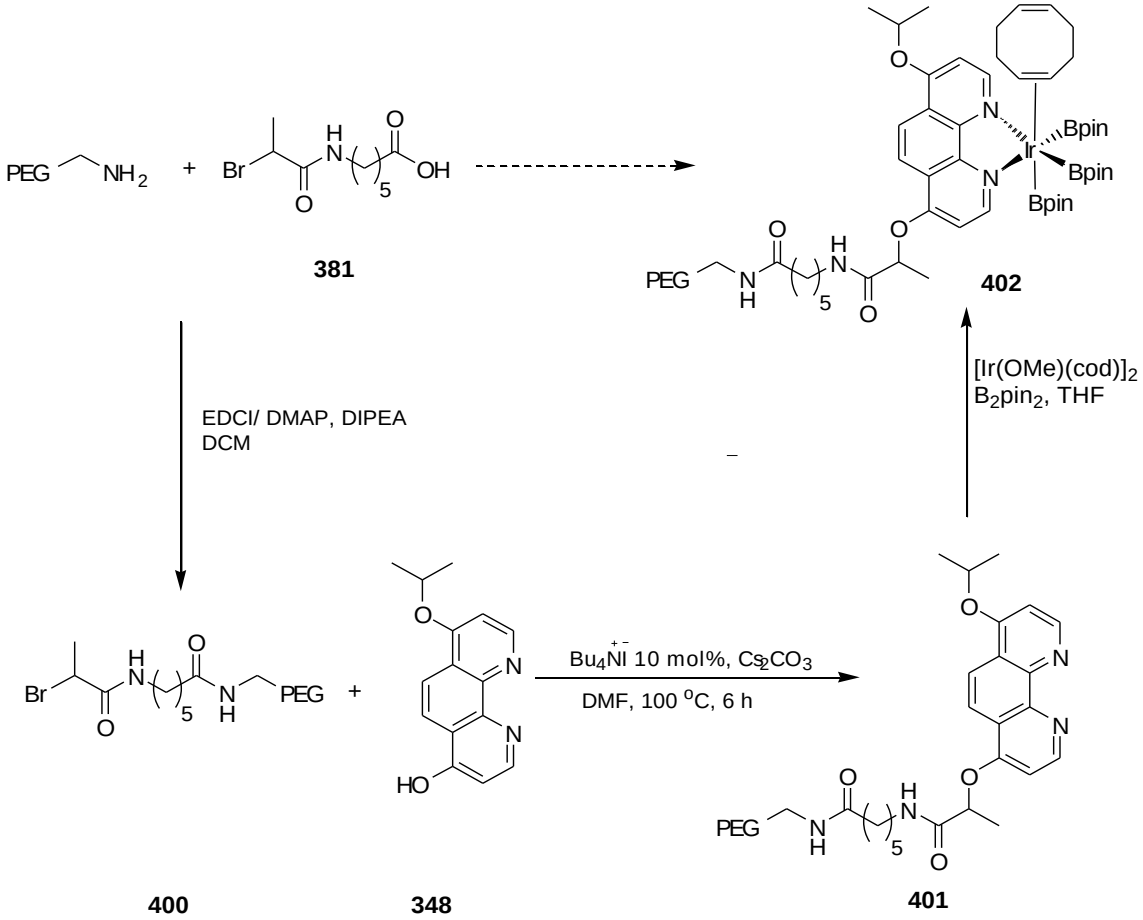
5.1.6 Future work

With the failure to develop the MCM-41 supported iridium catalyst, attention will turn towards immobilizing the ligand **368** on different resins. As before, the main criterion was a resin lacking aromatic rings, which could be borylated. PEG resins with terminal amines such as amine PEG A could be directly attached to the ligand. The amine PEG A is commercial available with good amine loading (0.35 mmol/g) and could be coupled with the lithium phenanthroline-carboxylate **368** or with the long chain-carboxylic acid **381** and alkylated with mono-ether **348**. In both cases, the resulting PEG supported ligand **398** and **401** could be coordinated with iridium catalyst to generate the active tris-boryliridium catalyst **399** (**Scheme 113**) and **402** and (**Scheme 114**).



368 **398** **399**

Scheme 113: Preparation of the active tris-boryliridium catalyst 399



400 **348** **401**

Scheme 114: Preparation of the active tris-boryliridium catalyst 402

5.1.7 In conclusion

In this work, symmetrical phenanthroline **347** and the mono-alkylated **348** could be prepared by Altman's procedure using different equivalents of 2-iodopropane. **348** could then be converted to phenanthroline ester **367** in good yield. Attempts to introduce a linker at the 5-position of phenanthroline **350** and **351** by either Suzuki-Miyaura cross coupling or reduction of the nitrile group were unsuccessful. Ligands **347** and **367** showed comparable activity to the commercially available tmphen ligand for the borylation of m-xylene (**Table 43**,**Table 44**). A phenanthroline ligand with a suitable linker **367** and **368** was sucucessfully achieved. Coupling of amine-tri-methoxysiliane **373** with ester **367** to generate amide **374** was not successful, while coupling of lithium carboxylate **368** with amine **392** was successfuly prepared using HBTU reagent**.** Unfortunately, low loading of the Fmoc onto MCM-41 led to decreased loading of the phenanthroline ligand onto MCM-41. Disappointingly, no borylation of m-xylene was achieved using the MCM-41-supported iridium catalyst.

6 Experimental Procedures

6.1 General Considerations

Borylation reactions

All borylation reactions were carried out under a dry nitrogen atmosphere using standard Schlenk techniques. Glassware was dried in oven before using in the borylation reaction. Solvents were anhydrous and degassed 3 times using freeze-pump.

Coupling reactions

Solvents were used without drying and degassed 3 times using freeze-pump.

Solvents

Anhydrous methyl-tert-butyl-ether (MTBE) was purchased from Sigma Aldrich. DMF and DMA were purchased from Sigma Aldrich. All other reaction solvents were dried using an Innovative Technology Solvent Purification System (SPS) and stored under Argon.

Reagents

$[Ir(OMe)(cod)]_2$ was prepeared according to a procedure described,[132] from $IrCl_3.3H_2O$, obtained from Precious Metals Online. B_2pin_2 was received as a generous donation from Allychem Co. Ltd. (P.R.China) and was used without purification. All other reagents were supplied from Alfa-Aesar, Apollo Scientific, Fluorochem, Acros, Sigma-Aldrich or Lancaster.

Microwave Reactor

All microwave reactions were carried out in septum-containing, crimp-capped, sealed vials in a monomodal Emrys^{TM} Optimizer reactor from Personal Chemistry. The wattage was automatically adjusted to maintain the desired temperature for the desired period of time.

NMR Spectroscopy

NMR spectra were recorded at ambient temperature on Varian VNMRS (^{13}C); Bruker Avance-400 (^{1}H), Varian VNMRS-700 (^{1}H, ^{13}C[^{1}H], HSQC, HMBC, COSY) or Varian Inova-600 (^{1}H, ^{13}C[^{1}H], HSQC, HMBC, COSY) spectrometers. The ^{1}H and ^{13}C chemical shifts are reported in ppm using the residual solvent signal of the deuterated solvents ($CDCl_3$: δ_H = 7.26 ppm, δ_c = 77.16; Benzene d_6: δ_H 7.16 ppm, δ_c = 128.06; DMSO d_6: δ_H = 2.50 ppm, δ_c = 39.52 ppm; Methanol d_4: δ_H = 3.31 ppm, δ_c = 49.00 ppm; NaOD: δ_H = 4.79 ppm). All chemical shifts are reported in parts per million relative to tetra-methylsilane (δ_H = 0.00 ppm). All coupling constants are reported in Hz. Multiplicities are reported using the following abbreviations; s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), hep (heptet), m (unresolved multiplet). Assignment of spectra was carried out using 2D COSEY, HSQC, HMBC and NOESY techniques.

Elemental Analysis

CHN Analysis was performed on a Exter Analytical CE-440 Elemental Analyzer.

IR Spectroscopy

Infrared spectra were measured on a Perkin-Elmer Paragon 1000 FT-IR spectrometer via the use of a Diamoned ATR (attenuated total reflection) accessory (Golden Gate). Assigned peaks are reported in wavenumbers (cm^{-1}).

Thin-Layer Chromatography (TLC)

TLC was performed on "Polygram Sil G/UV" plastic-backed silica plates with a 0.2 mm silica gel layer doped with a fluorescent indicator. Plates were purchased from VWR International.

Flash Column Chromatography

Flash column chromatography refers to purification by automated operation using a Teledyne Isco CombiFlash RF machine on pre-packed silica Redisep® Rf cartridges with the stated solvent gradient and at a constant flow rate of 35 mL/min. Reverse phase chromatography used pre-packed C_{18} silica Redisep® Rf cartridges and a 0-100% MeOH in H_2O (containing 0.1% HCOOH) gradient elution.

Mass Spectroscopy

GC-MS analyses were performed on an Agilent 6890N gas chromatography (column: HP-5MS, 10 m, Ø 0.25 mm, film 0.25 µm; injector: 250 ^oC; oven: 70 ^oC(2 min), 70 ^oC to 250 ^oC (20 ^oC min^{-1}), 250 ^oC (5 min); carrier gas: helium (1.6 mL min^{-1}) equipped with an Agilent 5973 inert mass selective detector operating in EI mode and a custom built Anatune liquid handling system functioning as autosampler/injector. Electrospray (ES)

mass spectra were obtained on a Micromass LCT Mass Spectrometer. High Resolution mass spectra were obtained using a Thermo Finnigan LTQFT mass spectrometer or Xevo QToF mass spectrometer (Waters UK, LTd) by the Durham University Mass Spectrometry Service.

Melting Point

Melting points were recorded using an Electrothermal 9100 capillary melting point apparatus.

UV-Vis-Spectrometry

Measurements were performed on a Unicam UV-Vis Spectrometer UV2.

6.2 Experimental details

Chapter 2

6.2.1 General Procedure for the Preparation of Stock Solution for C-H Borylation

In a glove box, supplied with inert gas atmosphere, a mixture of $[Ir(OMe)cod]_2$ (0.1 g, 0.15 mmol), dtbpy (0.08 g, 0.3 mmol) and B_2pin_2 (2.54 g, 10 mmol) was prepared in MTBE or THF (25 ml) by shaking vigorously in a volumetric flask. The resulting deep red coloured solution was then stored in a sealed tube at −20 °C.

6.2.2 Borylation of quinoline derivatives

6.2.2.1 Protocol A1:

The starting material, test substrate, (1.0 mmol) was placed in a reaction vessel, which was then sealed, evacuated under vacuum, backfilled with N_2. A 2.5ml aliquot of the borylation stock solution containing $[Ir(OMe)cod]_2$ (1.5 mol%), dtbpy (3 mol%) and B_2pin_2 (1 mmol) was added to the reaction vessel.

6.2.2.2 Protocol A2:

A mixture of the catalyst $[Ir(OMe)cod]_2$ (X mmol, X mol%), dtbpy (2X mmol, 2X mol%), B_2pin_2 (X mmol) and the test substrate (1.0 mmol) were placed in the reaction vessel which was then sealed, evacuated, backfilled with N_2 followed by addition of THF (2ml).

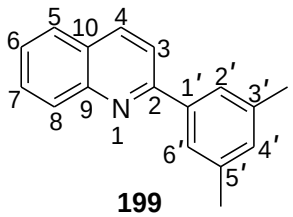
The reaction mixtures were then either heated up in a microwave reactor or under refluxe, subsequently, the reactions were quenched by adding DCM and the solvents were removed *in vacuo* to afford the crude products.

6.2.3 Preparation of 2-(aryl substitution)-quinoline

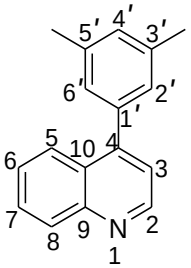
6.2.3.1 Baran Procedures B:[82]

6.2.3.1.1 *2-(3',5'-Di-methylphenyl)-quinoline* (199) [133]

6.2.3.1.2 *4-(3',5'-Di-methylphenyl)-quinoline* (200)[134]



199



200

A mixture of silver (I) nitrate (67.9 mg, 0.4 mmol) in water (0.5 ml) and $K_2S_2O_8$ (0.81 g, 3 mmol) was added to a mixture of quinoline **111** (0.118 ml, 1 mmol), TFA (77 µL, 1 mmol) and 3,5-di-methylphenylboronic acid **198** (0.6 g, 4 mmol) in biphasic DCM (5 ml) and water (3 ml). The mixture was stirred at room temperature for 12 h. An equivalent amount of $AgNO_3$ and $K_2S_2O_8$ was added again if arylboronic acids not dissolve totally after 3 h. A mixture of DCM (12 ml) and (5%) $NaHCO_3$ (20 ml) was then added to dilute and wash the solution respectively. The crude mixture was extracted with DCM, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on silica gel (1:3 EtOAc:hexane) afforded two isomers: 2-(3',5'-di-methylphenyl)-quinoline **199** was isolated as a green oil (0.08g, 34%); **Product 199:** rf 1: 3 EtOAc:hexane = 0.22; υ_{max} (ATR) 1594, 1556, 1503, 1376, 1315, 1206, 856, 823, 788, 754, 700, 678, 624 cm^{-1}; δ_H

(700 MHz, $CDCl_3$) 8.2 (1H, d, *J* = 8.4 Hz, 8-*H*), 8.2 (1H, *J* = 8.5 Hz, 4-*H*), 7.8 (1H, d, *J* = 8.5 Hz, 3-*H*), 7.82-7.79 (3H, m, 5-H, 2',6'-*H*), 7.7 (1H, ddd, *J* = 8.4 Hz, *J* = 6.8 Hz, 1.5 Hz, 7-*H*), 7.5 (1H, dd, *J* = 8.0 Hz, *J* = 6.8 Hz, 6-*H*), 7.1 (1H, s, 4'-*H*), 2.5 (6H, s, 3'-CH_3, 5'-CH_3); δ_C (176 MHz, $CDCl_3$) 157.6 (*C*-2), 148.1 (*C*-9), 139.5 (*C*-1'),138.2 (*C*-3',5'), 136.5 (*C*-4), 130.9 (*C*-4'), 129.5 (*C*-8), 129.4 (*C*-7), 127.3 (*C*-5), 127.0 (*C*-10), 126.0 (*C*-6), 125.3 (*C*-2',6'), 119.1 (*C*-3), 21.3 (*C*-2-(*C*H_3)$_2$); *m/z* (GC-MS, EI^+) 234 ($[MH]^+$, 17.9%), 233 ($[M]^+$, 100%), 232 ($[M-H]^+$, 49.7%), 217 ($[M-CH_4]^+$, 27%).

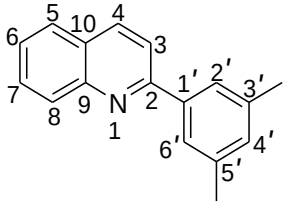
Furthermore, 4-(3',5'-di-methylphenyl)-quinoline **200** was isolated as a yellow oil (0.09 g, 39%); **product 200** rf 1:3 EtOAc:hexane = 0.5; υ_{max} (ATR) 1600, 1581, 1564, 1506, 1390, 1288, 1029, 843, 762, 729, 704,638 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.9 (1H, d, *J* = 4.2 Hz, 2-*H*), 8.2 δ (1H, dm, *J* = 8.4 Hz, 8-*H*), 7.9 (1H, dm, *J* = 8.4 Hz, 5-*H*), 7.7 (1H, ddd, *J* = 1.4 Hz, *J* = 7 Hz, *J* = 8.4 Hz, 7-*H*), 7.5 (1H, ddd, *J* = 1.4 Hz, *J* = 7 Hz, *J* = 8.4 Hz, 6-*H*), 7.3 (1H, d, *J* = 4.2 Hz, 3-*H*), 7.1 (1H, s, 4'-*H*), 7.1 (2H, s, 2',6'-*H*), 2.4 (6H, s, 3',5'-CH_3); δ_C (700 MHz, $CDCl_3$) 150.1 (*C*-2), 149.0 (*C*-4), 148.8 (*C*-9) 138.3 (*C*-3',5'), 138.1 (*C*-1'), 130.1 (*C*-4'), 130.0 (*C*-8), 129.3 (*C*-7), 127.4 (*C*-2',6'), 127.0 (*C*-10), 126.6 (*C*-6), 126.2 (*C*-5), 121.3 (*C*-3), 21.5 (*C*-2-(*C*H_3)$_2$); *m/z* (GC-MS, EI^+) 234 ($[MH]^+$, 48.7%), 233 ($[M]^+$, 100%), 232 ($[M-H]^+$, 66.7 %), 218 ($[M-CH_3]^+$, 100%), 203 ($[M-2CH_3]^+$, 15%), 189 (14%), 176 (4%).

6.2.3.2 Suzuki-Miyaura Cross-Coupling general procedure C:[84]

Under N_2, a mixture of 2-halo heteroaromatic (1 eq.), arylboronic acid (3.0 equiv) and $Pd(PPh_3)_4$ (X mol%) was dissolved in a degased mixture of toluene (3 ml) and 2 M (aq.) potassium carbonate (1.1 ml) in a closed microwave vessel. The mixture was heated in the microwave for the stated time at 160 ^oC and then cooled to room temperature.

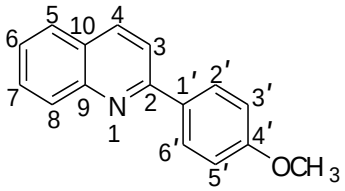
The crude mixture was then washed with $NaHCO_3$ (aq.) solution and extracted with EtOAc (2 × 20 ml). The combined organic extracts were then back extracted using 1 M hydrochloric acid. The aqueous layers were then neutralized (pH = 7) with 1 M sodium hydroxide and then extracted with ether (3×10 ml). The organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to afford the title biaryl compound.

6.2.3.2.1 *2-(3',5'-Di-methylphenyl)-quinoline* (199)[133]



Following Suzuki-Miyaura cross-coupling procedure **C**, 2-chloroquinoline **203** (36.8 mg, 0.39 mmol) was reacted with 3,5-di-methylphenylboronic acid **198** (177 mg, 1.17 mmol) in the presence of $Pd(PPh_3)_4$ (10 mol%), heated for 10 min to afford the title biaryl 2-(3',5'-di-methylphenyl)-quinoline **199** as a green oil (69 %); Data have been identified above in **6.2.3.1.1**.

6.2.3.2.2 *2-(4'-Methoxyphenyl)-quinoline* (205)[135]



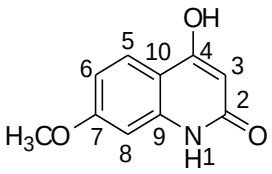
Following Suzuki-Miyaura cross-coupling procedure **C**, 2-chloroquinoline **203** (36.8 mg, 0.39 mmol) was reacted with 4-methoxyphenylboronic acid **5** (177.8 mg, 1.17 mmol) in

the presence of $Pd(PPh_3)_4$ (5 mol%) to afford after heating for (1 h) the title biaryl 2-(4'-methoxyphenyl)-quinoline **205** as a brown solid (85 %), (mp = 121-122 ^oC, lit.,[135] 123.7-125.6 ^oC); υ_{max} (ATR) 1596, 1550, 1497, 1430,1248, 1175, 1027,815, 789, 748,726 cm^{-1}; δ_H (600 MHz, C_6D_6) 8.4 (1H, d, *J* = 8.4 Hz, 8-*H*), 8.32-8.27 (2H, m, 2'-H, 6'-*H*), 7.7 (1H, d, *J* = 8.6 Hz, 4-*H*), 7.5 (1H, d, *J* = 8.6 Hz, 3-*H*), 7.5 (1H, d, *J* = 8.1 Hz, 5-*H*), 7.4 (1H, ddd, *J* = 8.4, *J* = 6.8 Hz, *J* = 1.5 Hz, 7-*H*), 7.21-7.17 (1H, m, 6-*H*), 7-6.9 (2H, m, 3',5'-*H*), 3.3 (3H, s, OCH_3); δ_C (151 MHz, C_6D_6) 161.6 (*C*-4'), 157.1 (*C*-2), 149.3 (*C*-9), 136.6 (*C*-4), 132.8 (*C*-1'), 130.4 (*C*-8), 129.8 (*C*-7), 129.5 (*C*- 2',6'), 127.8 (*C*-5), 127.5 (*C*-10), 126.1 (*C*-6), 118.5 (*C*-3), 114.6 (*C*-3',5'), 55 ($C\text{-}OCH_3$); *m/z* (GCMS, EI^+) 236 ($[MH]^+$, 18%), 235 ($[M]^+$, 100%), 220 ($[M\text{-}CH_3]^+$, 29%), 204 ($[M\text{-}OCH_3]^+$, 4%), 191 (30%).

6.2.4 Preparation of quinoline 2,4-dione derivatives, procedure D[85]

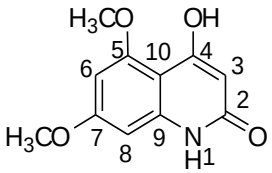
In a round bottom flask, a mixture of malonic acid (1.1 eq.), $POCl_3$ (1 eq.) and an aniline derivative (1 eq.) was heated with stirring at 50 ^oC for 2 h. The temperature was then increased slowly to 90 ^oC over 30 min and the reaction was heated for another 30 min. Upon cooling down the reaction mixture to room temperature, 0.5 M sodium hydroxide was initially added to render the pH basic (pH = 14) followed by addition of concentrated hydrochloric acid (HCl) to render the solution acidic (pH = 2-3) causing the product to precipitate. The resultant precipitate was collected by filtration, washed with water and dried in a desiccator. The product was purified by trituration with ethanol to yield the desired quinoline-2,4-dione derivative.

6.2.4.1 *4-Hydroxy-7-methoxyquinoline-2-one* (211)[136]



Following procedure **D**, malonic acid **208** (2.6 g, 25.2 mmol), $POCl_3$ (2.2 ml, 23.9 mmol) and m-anisidine **209** (2.7 ml, 23.9 mmol) were used in order to afford 4-hydroxy-7-methoxyquinoline-4-one **211** as a white solid (2.0 g, 43%), (mp > 300 ^oC, lit.,[136] >300 ^oC); υ_{max} (ATR) 3000-2672 (broad, NH), 2612 (OH), 1626 (C=O), 1600, 1552, 1509, 1463, 1435, 1379, 1329, 1246, 1214, 1183, 1151, 1015, 802, 733, 632 cm^{-1}; δ_H (700 MHz, d_6-DMSO) 11.1 (1H, bs, O*H*), 11.0 (1H, bs, N*H*), 7.7 (1H, d, *J* = 8.7 Hz, 5-*H*), 6.8 (1H, d, *J* = 2.4 Hz, 8-*H*), 6.7 (1H, dd, *J* = 2.4 Hz, *J* = 8.7 Hz, 6-*H*), 5.6 (1H, s, 3-*H*), 3.8 (3H, s, OCH_3); δ_C (176 MHz, d_6-DMSO) 163.9 (*C*-2), 162.5 (*C*-4), 161.4 (*C*-7), 141.0 (*C*-9), 124.1 (*C*-5), 109.7 (*C*-8), 108.8 (*C*-10), 97.9 (*C*-6), 95.9 (*C*-3), 55.3 (7-O*C*H_3); *m/z* (LC-MS, ES^+) 383 ($[M_2H]^+$), (192 $[MH]^+$).

6.2.4.2 *4-Hydroxy-5, 7-di-methoxyquinoline-2-one* (212)

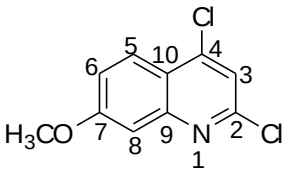


Following procedure **D**, malonic acid **208** (2.6 g, 25.2 mmol), $POCl_3$ (2.2 ml, 23.9 mmol) and 3,5-di-methoxy aniline **210** (3.7 g, 23.9 mmol) was used in order to afford 4-hydroxy-5,7-di-methoxyquinoline-2-one **212** as a brown powder (2.61 g, 49 %), (mp = 248-249 ^oC); υ_{max} (ATR) 2969-2875 (broad OH), 3308 (NH), 1645 (C=O), 1606, 1573,1452, 1421, 1390, 1229, 1202, 1197, 1135, 1049, 966, 819, 770 cm^{-1}; δ_H (700

MHz, d_6-DMSO) 11.1 (1H, bs, N*H*), 9.8 (1H, bs, O*H*), 6.4 (1H, d, *J* = 2.3 Hz, 8-*H*), 6.3 (1H, *d*, *J* = 2.3 Hz, 6-*H*), 5.4 (1H, s, 3-*H*), 3.9 (3H, s, 5-OC*H*$_3$), 3.8 (3H, s, 7-OC*H*$_3$); δ_C (176 MHz, d_6-DMSO) 163.6 (*C*-2 or *C*-4), 163.3 (*C*-4 or *C*-2), 161.8 (*C*-7), 158.0 (*C*-5), 142.6 (*C*-9), 98.4 (*C*-10), 96.4 (*C*-3), 93.1 (*C*-6), 91.2 (*C*-8), 56.3 (5-OCH_3), 55.4 (7-OCH_3) *m/z* (LCMS, ES$^+$) 443 ([M_2H]$^+$), 222 ([MH]$^+$), 221 ([M]$^+$); HRMS (ASAP) found ([MH]$^+$) 222.0769, $C_{11}H_{12}NO_4$ requires M, 222.0766.

6.2.5 *2,4-Di-chloroquinoline derivatives*[87]

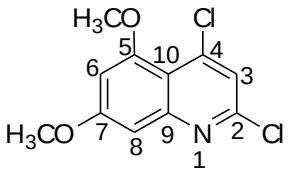
6.2.5.*1* *2,4-Di-chloro-7-methoxyquinoline* (213)[137]



4-Hydroxy-7-methoxyquinoline-2-one **211** (23.8 mg, 0.125 mmol) was dissolved in excess $POCl_3$ (0.9 ml, 1 mmol). The mixture was then heated for 1 h at 105 ^{o}C. The solution was then cooled down in an ice bath followed by addition of water (15 ml) and ammonium hydroxide (aq.) to neutralize the solution (pH = 7), causing the product to precipitate. The resultant solid was collected by filtration, washed with water and dried in a desiccator to afford the quinoline derivative **213** as a yellow powder (27 mg, 95%), (mp = 134-135 ^{o}C, lit.,[137] 132-133 ^{o}C); υ_{max} (ATR) 3094, 1623, 1573, 1496, 1454, 1439, 1224, 1091, 1024, 846, 819, 738, 698, 623 cm^{-1} ;δ_H (700 MHz, $CDCl_3$) 8.1 (1H, d, *J* = 9.2 Hz, 5-*H*), 7.4 (1H, s, 3-*H*), 7.3 (1H, d, *J* = 2.6 Hz, 8-*H*), 7.3 (1H, dd, *J* = 2.6 Hz, *J* = 9.2 Hz, 6-*H*), 3.9 (3H, s, OC*H*$_3$); δ_C (176 MHz, $CDCl_3$) 162.6 (*C*-7), 150.6 (*C*-2), 150.5 (*C*-9), 144.4 (*C*-4), 125.6 (*C*-5), 121.2 (*C*-6), 120.5 (*C*-10), 119.9 (*C*-3), 107.5 (*C*-8), 56.1 (7-O*C*H$_3$) ; *m/z* (GC-MS, EI$^+$) 231 ([M (^{37}Cl,^{37}Cl)-H]$^+$, 10%), 229 ([M (^{35}Cl, ^{37}Cl)-H]$^+$, 65%), 228

([M (^{35}Cl,^{35}Cl)]$^{+}$, 12%), 227 ([M (^{35}Cl,^{35}Cl)-H]$^{+}$, 100%), 212 ([M (^{35}Cl,^{35}Cl)-CH_4]$^{+}$, 3%), 197 ([M (^{35}Cl,^{35}Cl)-OCH_3]$^{+}$, 17%), 184 (40%), 162 ([M (^{35}Cl)-OCH_3-(^{35}Cl)]$^{+}$, 35%), 157 ([M-H-(^{35}Cl,^{35}Cl)]$^{+}$, 12%).

6.2.5.2 *2,4-Di-chloro-5,7-di-methoxyquinoline* (214)[138]



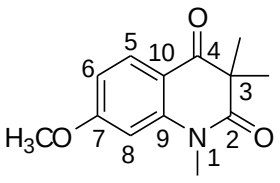
In a round-bottomed flask, a mixture of malonic acid **208** (520 mg, 5 mmol), $POCl_3$ (4.2 ml, 45 mmol) and 3,5-di-methoxy aniline **210** (766 mg, 5 mmol) was heated with stirring at 50 ^{o}C for 2 h. The temperature was then increased slowly over 30 min to 90 ^{o}C and the reaction was heated for another 30 min before the temperature was then raised to 105 ^{o}C and the mixture was heated for a further 1 h. The reaction was then cooled down in an ice bath and water (15 ml) was added. Ammonium hydroxide (aq.) was then added to neutralize the solution, causing the product to precipitate (pH = 7). The resultant solid was collected by filtration, washed with water and dried in a desiccator. The crude product was then re-dissolved in $POCl_3$ (4.2 ml) and heated at 105 ^{o}C for 2 h. The solution was then cooled in an ice bath and precipitated by adding Ammonium hydroxide (aq.). The resultant solid was collected by filtration, washed with water and dried in a desiccator. The product was purified by recrystallization from ethanol to afford 2,4-di-chloro-5,7-di-methoxyquinoline **214** as a brown powder (0.92 g, 71 %), (mp = 167-168 ^{o}C, lit.,[138] 172-173 ^{o}C); υ_{max} (ATR) 1613, 1575, 1557, 1455, 1394,1351, 1212, 1143,973, 828, 686 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 7.2 (1H, s, 3-*H*), 6.9 (1H, d, *J* = 2.4 Hz, 8-*H*), 6.5 (1H, d, *J* = 2.4 Hz, 6-*H*), 3.91 (3H, s, 5-OC*H*$_3$), 3.90 (3H, s, 7-

OC*H*$_3$); δ_C (176 MHz, $CDCl_3$) 162.3 (*C*-7), 157.3 (*C*-5), 152.2 (*C*-9), 150.4 (*C*-2), 143.1 (*C*-4), 121.1 (*C*-3), 113.1 (*C*-10), 100.5 (*C*-8), 100.3 (*C*-6), 56.1 (C-5-OCH_3), 55.8 (C-7-OCH_3); *m/z* (LC-MS, ES^+) 262 ([M (^{37}Cl,^{37}Cl)]$^+$, 14%), 260 ([M (^{35}Cl,^{37}Cl),]$^+$, 67%), 258 ([M (^{35}Cl,^{35}Cl)]$^+$100%).

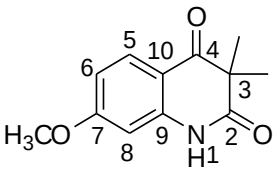
6.2.6 Methylation procedure[86]

6.2.6.1 *N-Methyl-3,3-di-methyl-7-methoxyquinoline-2,4-dione* (225)[139]

6.2.6.2 *3,3-Di-methyl-7-methoxyquinoline-2,4-dione* (226)



225



226

A mixture of 4-hydroxy-7-methoxyquinoline-2-one **211** (100 mg, 0.5 mmol) and sodium hydride 60% dispersion in mineral oil (32.0 mg, 0.8 mmol) in dry DMF (6 ml) was stirred for 30 min and then heated at 100 ^oC for 5 min. Methyl iodide (163 µl, 2.6 mmol) was then added to the stirring mixture and the reaction was further heated for 2 h at 100 ^oC. The solution was cooled down and then poured unto ice-water (20 ml). The crude mixture was extracted with EtOAc (2 × 10 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Purification using chromatography on silica gel (2:3 EtOAc:hexanes) afforded *N*-methyl-3,3-di-methyl-7-methoxyquinoline-2,4-dione **225** as a yellow solid (9 mg, 7%), (mp = 84-85 ^oC, lit.,[139] 89-90 ^oC). **Product 225** Rf 2:3 EtOAc:hexane = 0.36; υ_{max} (ATR) 1693 (C=O), 1656 (C=O), 1602, 1470, 1332, 1313, 1098, 1038, 799, 730 cm^{-1} ; δ_H (700 MHz, $CDCl_3$), 8.0 (1H, d, *J* = 8.7 Hz, 5-*H*), 6.7 δ (1H, dd, *J* = 2.2 Hz, *J* = 8.7 Hz, 6-*H*), 6.6

(1H, d, *J* = 2.2 Hz, 8-*H*) 3.9 (3H, s, OCH_3), 3.4 (3H, s, N-CH_3), 1.5 (6H,s, 3-(CH_3)$_2$); δ_C (176 MHz, $CDCl_3$) 196.5 (*C*-4), 175.2 (*C*-2), 166.1 (*C*-7), 145.4 (*C*-9), 131.1 (*C*-5), 114 (*C*-10), 108.4 (*C*-6), 101.1 (*C*-8), 56.1 (7-O*C*H$_3$), 52.9 (*C*-3), 30.2 (N-*C*H$_3$), 24.6 (3-(*C*H$_3$)$_2$); *m/z* (GC-MS, EI$^+$) 234 ([MH]$^+$, 14%), 233 ([M]$^+$, 96%), 218 ([M-CH$_3$]$^+$, 17%), 204 ([MH-2CH$_3$]$^+$, 9%), 190 (17%), 163 (100%), 134 (44%).

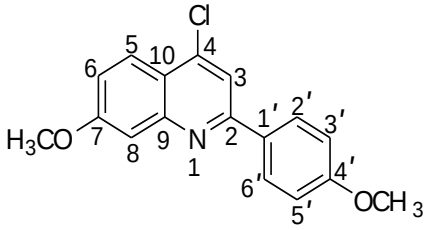
Furthermore, 3,3-di-methyl-7-methoxyquinoline-2,4-dione **226** was isolated as a white solid (40.9 mg, 35%), (mp = 160-161 ^{o}C), Rf 2:3 EtOAc:hexane = 0.21; υ_{max} (ATR) 3246 (NH), 2934, 1698 (C=O), 1651(C=O), 1606, 1590, 1483, 1462, 1381, 1336, 1264, 1208, 1116, 1032, 850, 810, 775 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 9.1(1H, bs, N*H*), 7.9 (1H, d, *J* = 8.4 Hz, 5-*H*), 6.7 (1H, dd, *J* = 2.1 Hz, *J* = 8.4 Hz, 6-*H*), 6.4 (1H, d, *J* = 2.1 Hz, 8-*H*), 3.9 (3H, s, OCH_3), 1.5 (6H, s, 3-(CH_3)$_2$); δ_C (176 MHz, $CDCl_3$) 196.2 (*C*-4), 176.8 (*C*-2), 166.0 (*C*-7), 142.9 (*C*-9), 130.5 (*C*-5), 112.3 (*C*-10), 110.6 (*C*-6), 100.3 (*C*-8), 55.9 (7-O*C*H$_3$), 52.4 (*C*-3), 23.9 (3-(*C*H$_3$)$_2$); *m/z* (GC-MS, EI$^+$) 220 ([MH]$^+$, 13.7%), 219 ([M]$^+$, 100%), 218 ([M-H]$^+$, 27%), 204 ([M-CH$_3$]$^+$, 52%), 191 (13%), 176 (21%), 149 (72%), 122 (25%).

6.2.7 Preparation of 2-(aryl substitution)-4-,5- and 7-substituted quinoline derivatives Procedure E:[84]

Under N_2, a mixture of 2,4-di-halo heteroaromatic substrate (1 eq.), arylboronic acid (1-1.5 eq.) and $Pd(PPh_3)_4$ 5 mol% was dissolved in a degased mixture of toluene or DMF (4.1 ml) and 2 M K_2CO_3 (aq.) (1.4 ml) in closed microwave vessel. The mixture was heated in a microwave oven at 100 ^{o}C for the stated time and then cooled to room temperature. The crude mixture was then washed with $NaHCO_3$ (aq.) solution and

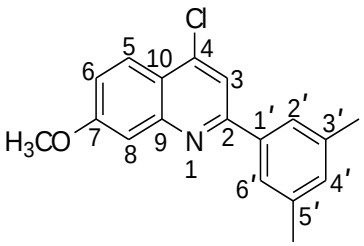
extracted with EtOAc or DCM (2 × 20 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography afforded the title biaryl compound.

6.2.7.1 *2-(4'-Methoxyphenyl)-4-chloro-7-methoxyquinoline* (230)



Following procedure **E**, 2,4-di-chloro-7-methoxyquinoline **213** (501.6 mg, 2.2 mmol), 4-methoxyphenylboronic acid **5** (499.4 mg, 3.3 mmol) and $Pd(PPh_3)_4$ (125.4 mg, 0.11 mmol) were heated in toluene for 2.5 h. Following purification by chromatography (EtOAc:hexane 1:4), 2-(4'-methoxyphenyl)-4-chloro-7-methoxyquinoline **230** was obtained as a white coloured foam (0.49g, 75 %), (mp =102-103 ^oC); υ_{max} (ATR) 1607, 1577, 1498, 1447, 1425, 1396, 1372, 1332, 1247, 1215, 1175, 1132, 1028, 970, 838, 820, 814, 700, 676, 645 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.1-8.8 (1H, m, 5-*H*), 8.8-8.0 (2H, m, 2',6'-*H*), 7.8 (1H, s, 3-*H*), 7.5 (1H, d, *J* = 2.5 Hz, 8-*H*), 7.22 (1H, dd, *J* = 9.1 Hz, *J* = 2.5Hz, 6-*H*), 7.1-7.0 (2H, m, 3',5'-*H*), 4.0 (3H, s, 7-OC*H*$_3$), 3.9 (3H, s, 4'-OC*H*$_3$); δ_C (176 MHz, $CDCl_3$) 161.7 (*C*-7), 161.2 (*C*-4'), 157.5 (*C*-2), 151.0 (*C*- 9), 142.9 (*C*-4), 131.4 (*C*-1'), 129.0 (*C*-2', 6'), 125.2 (*C*-5), 120.2 (*C*-6), 120.1 (*C*-10), 114.4 (*C*-3',5'), 107.8 (*C*-8), 55.8 (C-7-O*C*H_3), 55.6 (C-4'-O*C*H_3); *m/z* (GC-MS, EI^+) 301 ([M (^{37}Cl)]$^+$, 33.7%), 299 ([M (^{35}Cl)]$^+$, 100%), 284 ([M (^{35}Cl)-CH_3]$^+$, 12%), 270 ([MH (^{35}Cl)-2CH_3]$^+$, 2%), 264 ([M-(^{35}Cl)]$^+$, 5%), 256 (12%), 249 ([M-CH_3-(^{35}Cl)]$^+$, 5%); HRMS (ASAP) found ([MH]$^+$) 300.0783; $C_{17}H_{15}{}^{35}ClNO_2$ requires M, 300.0791.

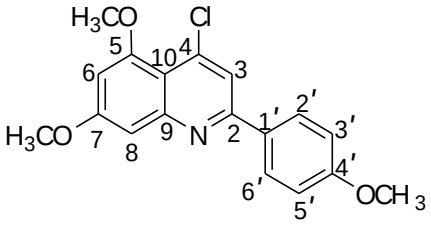
6.2.7.2 *2-(3', 5'-Di-methylphenyl)-4-chloro-7-methoxyquinoline* (233)



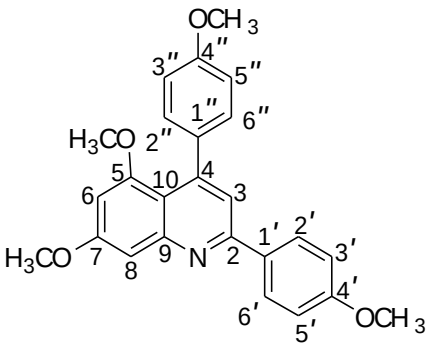
Following procedure **E**, 2,4-di-chloro-7-methoxyquinoline **213** (501.6 mg, 2.2 mmol), 3, 5-di-methylboronic acid **198** (330 mg, 2.2 mmol) and Pd $(PPh_3)_4$ (125.4 mg, 0.11 mmol) were heated in toluene for 30 min. Purification by chromatography (EtOAc:hexane 1:9), afforded 2-(3',5'-di-methylphenyl)-4-chloro-7-methoxyquinoline **233** was obtained as a white coloured foam (395 mg, 60 %), (mp =165-166 ^{o}C); υ_{max} (ATR) 1617, 1578, 1503, 1450, 1336, 1217, 1131, 1025, 847, 823, 706, 690, 635 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 8.1 (1H, d, *J* = 9.1 Hz, 5-*H*), 7.8 (1H, s, 3-*H*), 7.7 (2H, m, 2',6'-*H*), 7.5 (1H, d, *J* = 2.5 Hz, 8-*H*), 7.24 (1H, dd, *J* = 9.1 Hz, *J* = 2.5Hz, 6-*H*), 7.13-7.09 (1H, m, 4'-*H*), 4.0 (3H, s, 7-O*C*H_3), 2.43 (6H, s, 3',5'-CH_3); δ_C (151 MHz, $CDCl_3$) 161.6 (*C*-7), 158.2 (*C*-2), 151.0 (*C*-9), 142.8 (*C*-10), 138.8 (*C*-1'), 138.5 (*C*-3',5'), 131.5 (*C*-4'), 125.4 (*C*-2',6'), 125.1 (*C*-5), 120.5 (*C*-4), 120.3 (*C*-6), 117.3 (*C*-3), 108.0 (*C*-8), 55.8 (C-7-O*C*H_3), 21.6 (3',5'-(*C*H_3)$_2$); *m/z* (LC-MS, ES^+) 300 ([M (^{37}Cl)]$^+$, 33%), 298 ([M (^{35}Cl)]$^+$, 100%); HRMS (ASAP) found ([MH]$^+$) 298.1009; $C_{18}H_{17}{}^{35}ClNO$ requires M, 298.0999.

6.2.7.3. *2-(4'-Methoxyphenyl)-4-chloro-5,7-di-methoxyquinoline* (234)

6.2.7.4 *2,4-Di-(4-methoxyphenyl)-5,7-di-methoxyquinoline* (235)



234



235

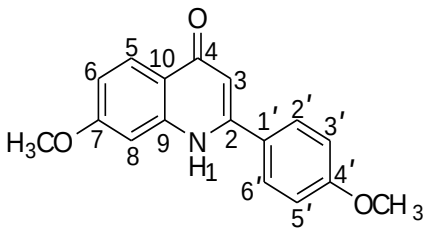
Following procedure **E**, 2,4-di-chloro-5,7-di-methoxyquinoline **214** (567.6 mg, 2.2 mmol), 4-methoxyphenylboronic acid **5** (384.5 mg, 2.53 mmol) and Pd $(PPh_3)_4$ (125.4 mg, 0.11 mmol) were heated in DMF for 1 h. Purification by chromatography (EtOAc:hexane 1:4), afforded 2-(4'-methoxyphenyl)-4-chloro-5,7-di-methoxyquinoline **234** was obtained as a yellow solid (0.23g, 32 %), (mp = 143-144 ^oC); υ_{max} (ATR) 1606, 1574, 1523, 1496, 1363, 1250, 1201, 1173, 1157, 1133, 1115, 1028, 857, 824, 792, 615 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.1 (2H, m, 2',6'-*H*), 7.7 (1H, s, 3-*H*), 7.1 (1H, d, *J* = 2.4 Hz, 8-*H*), 7.05-7.0 (2H, m, 3',5'-*H*), 6.5 (1H, d, *J* = 2.4 Hz, 6-*H*), 3.95-3.95 (3H, s, 7-OCH_3), 3.94 (3H, s, 5-OCH_3), 3.9 (3H, s, 4'-OCH_3); δ_C (176 MHz, $CDCl_3$) 161.4 (*C*-7), 161.2 (*C*-4'), 157.1 (*C*-5), 157.0 (*C*-2), 153.0 (*C*-9), 141.4 (*C*-4), 131.0 (*C*-1'), 128.9 (*C*-2',6'), 118.5 (*C*-3), 114.3 (*C*-3',5'), 112.9 (*C*-10), 101.1 (*C*-8), 99.6 (*C*-6), 56.0 (*C*-O*C*H_3), 55.7 (C-O*C*H_3), 55.5 (C-O*C*H_3); *m/z* (GC-MS, EI^+) 331 ([M (^{37}Cl)]$^+$, 33.9%), 329 ([M (^{35}Cl)]$^+$, 100%), 314 ([M-CH_3]$^+$, 4%), 300 ([MH-$(CH_3)_2$]$^+$, 9%), 294 ([M-(^{35}Cl)]$^+$, 3%), 286 (12%), 279 ([M-CH_3-(^{35}Cl)]$^+$, 2%), 271 ([MH (^{37}Cl)-O-3CH_3]$^+$ 6%), 265 ([MH-2CH_3-(^{35}Cl)]$^+$, 2%); HRMS (ASAP) found ([MH]$^+$) 330.0902; $C_{18}H_{17}{}^{35}ClNO_3$ requires M, 330.0897.

Similarly, 2,4-di-(4'-methoxyphenyl)-5,7-di-methoxyquinoline **235** was also isolated as a yellow solid (0.08g, 9 %), (mp = 157-158 ^{o}C); υ_{max} (ATR) 1606, 1582, 1516, 1346, 1296, 1261, 1240, 1224, 1178, 1170, 1026, 844, 830, 802, 679 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.13-8.09 (2H, m, 2',6'-*H*), 7.4 (1H, s, 3-*H*), 7.32-7.28 (2H, m, 2",6"-*H*), 7.2 (1H, s, 8-*H*), 7.04-6.99 (2H, m, 3',5'-*H*), 6.96- 6.89 (2H, m, 3",5"-*H*), 6.5 (1H, d, *J* 2.4 Hz, 6-*H*), 4 (3H, s, 7-OC*H*$_3$), 3.89 (3H, s, 4"-OC*H*$_3$), 3.87 (3H, s, 4'-OC*H*$_3$), 3.5 (3H, s, 5-OC*H*$_3$); δ_C (176 MHz, $CDCl_3$) 161.1 (*C*-5), 161.0 (*C*-4´), 159.0 (*C*-4"), 157.5 (*C*-7), 156.4 (*C*-2), 152.0 (*C*-9), 148.3 (*C*-4), 135.6 (*C*-1"), 132.1 (*C*-1'), 129.7 (*C*-2",6"), 129.0 (*C*-2',6'), 119.1 (*C*-3), 114.3 (*C*-3',5'), 113.6 (*C*-10), 112.6 (*C*-3",5"), 101.0 (*C*-8), 99.0 (*C*-6), 55.7 (C-7-O*C*H$_3$), 55.5 (*C*-O*C*H$_3$), 55.5 (*C*-O*C*H$_3$), 55.4 (*C*-O*C*H$_3$); *m/z* (GC-MS, EI$^+$) 403 ([M_2H]$^+$, 4.3%), 402 ([MH]$^+$, 26.2%), 401 ([M]$^+$, 100%), 386 ([M-CH_3]$^+$, 12%), 370 ([M-OCH_3]$^+$, 11%), 355 ([M-O-2CH_3]$^+$, 4%), 343 (4%), 327 (2%), 312 (2%); HRMS (ASAP) found ([MH]$^+$) 402.1697; $C_{25}H_{24}NO_4$ requires M, 402.1705.

6.2.8 Preparation of quinoline 4-one, procedure F[89]

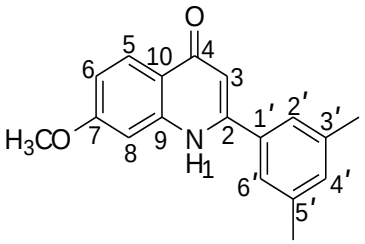
4-Chloroquinoline compounds **230, 233** and **234** (1 eq.) were heated in glacial acetic acid (26 eq.) at 125 ^{o}C for 1 h. The reaction mixture was then cooled to room temperature, causing the product to precipitate, and diluted with water (15 ml). 3 M sodium hydroxide was added to give a basic solution (pH= 8-9). The resultant solid was collected by filtration, washed with water and dried in a desiccator. The products were purified by trituration and dried *in vacuo*.

6.2.8.1 *2-(4'-Methoxyphenyl)-7-methoxyquinoline-4-one* (192B)



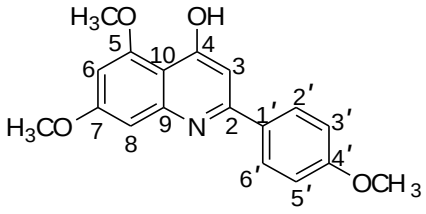
Following procedure **F,** compound **230** (23 mg, 0.077 mmol) was heated in glacial acetic acid. Following trituration with THF, 2-(4'-methoxyphenyl)-7-methoxyquinoline-4-one **192B** was obtained as a white powder (10 mg, 45 %), (mp = 302-303 ^{o}C); υ_{max} (ATR) 3241 (NH), 1626 (C=O), 1613, 1575, 1546, 1511, 1442, 1376, 1299, 1256, 1243, 1206, 1178,1140,1020, 831, 812 cm^{-1}; δ_H (700 MHz, d_6-DMSO) 11.4 (1H, s, N*H*), 8.0 (1H, d, *J* = 8.8 Hz, 5-*H*), 7.8 (2H, m, 2',6'-*H*), 7.2 (1H, d, *J* = 2.4 Hz, 8-*H*), 7.1 (2H, m, 3',5'-*H*), 6.9 (1H, dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 6-*H*), 6.2 (1H, s, 3-*H*), 3.86 (3H, s, 7-OC*H*$_3$), 3.85 (3H, s, 4'-OC*H*$_3$); δ_C (176 MHz, d_6-DMSO) 176.4 (*C*-4), 161.8 (*C*-7), 161.0 (*C*-4'), 149.2 (*C*-2), 142.2 (*C*-9), 128.6 (*C*-2',6'), 126.5 (*C*-5), 126.2 (*C*-1'), 119.1 (*C*-10), 114.4 (*C*-3',5'), 113 (*C*-6), 106.2 (*C*-3), 99.6 (*C*-8), 55.4 (C-7-O*C*H$_3$), 55.4 (*C*-4'-O*C*H$_3$); *m/z* (LC-MS, ES$^+$) 282 ([MH]$^+$), 562 ([M$_2$]$^+$); HRMS (ASAP) found ([MH]$^+$) 282.1120; $C_{18}H_{18}NO_4$ requires M, 282.1130.

6.2.8.2 *2-(3',5'-Di-methylphenyl)-7-methoxyquinoline-4-one* (240B)



Following procedure **F,** compound **233** (22.9 mg, 0.077 mmol) was heated in glacial acetic acid. Following trituration with hot EtOAc, 2-(3',5'-di-methylphenyl)-7-methoxyquinoline-4-one **240B** was obtained as a white powder (8 mg, 37 %), (mp = 265-266 ^{o}C); υ_{max} (ATR) 3069 (NH), 1619 (C=O), 1589, 1546, 1505, 1464, 1257, 1210, 1135, 1093, 1031, 853, 831, 715, 671, 624 cm^{-1}; δ_H (700 MHz, d$_4$-Methanol) 8.13 (1H, d, *J* = 9.0 Hz, 5-*H*), 7.4 (2H, m, 2',6'-*H*), 7.2 (1H, s, 4'-*H*), 7.5 (1H, d, *J* = 2.4 Hz, 8-*H*), 7.1 (1H, dd, *J* = 9.0 Hz, *J* = 2.4 Hz, 6-*H*), 6.4 (1H, s, 3-*H*), 3.93 (3H, s, 7-OC*H*$_3$), 2.41 (6H, s, 3',5'-C*H*$_3$); δ_C (176 MHz, d$_4$-Methanol) 180.2 (*C*-4), 164.7 (*C*-7), 153.4 (*C*-2), 143.9 (*C*-9), 140.2 (*C*-3',5'), 135.4 (*C*-1'), 133.3 (*C*-4'), 127.6 (*C*-5), 126.1 (*C*-2',6'), 120.0 (*C*-10), 116.0 (*C*-6), 108.0 (*C*-3), 100.1 (*C*-8), 56.2 (C-7-O*C*H$_3$), 21.3 (3',5'-(*C*H$_3$)$_2$); *m/z* (LC-MS, ES$^+$) 559 ([M$_2$H]$^+$), 280 ([MH]$^+$); HRMS (ASAP) found ([MH]$^+$) 280.1336; $C_{18}H_{18}NO_2$ requires M, 280.1338.

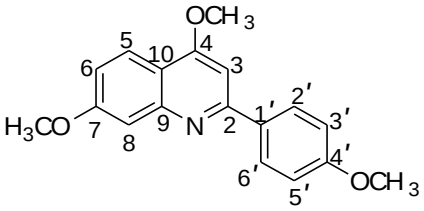
6.2.8.3 *2-(4'-Methoxyphenyl)-5,7-di-methoxyquinoline-4-ol* (241A)



Following procedure **F,** compound **233** (25 mg, 0.077 mmol) was heated in glacial acetic acid. Following trituration with ether, 2-(4'-methoxyphenyl)-5,7-di-methoxyquinoline-4-ol **241A** was obtained as a white powder (11 mg, 45 %), (mp = 233-234 ^{o}C); υ_{max} (ATR) 3360-2730 (broad OH), 1602, 1511, 1445, 1372, 1247, 1207, 1166, 1136, 1111, 1037, 827, 672 cm^{-1}; δ_H (600 MHz, Methanol-d$_4$) 7.7 (2H, m, 2',6'-*H*), 7.1 (2H, m, 3',5'-*H*), 6.7 (1H, s, 8-*H*), 6.4 (1H, s, 6-*H*), 6.3 (1H, s, 3-*H*), 4.6 (1H, s, OH), 3.9

(3H, s, 7-OC*H*$_3$), 3.88 (3H, s, 5-OC*H*$_3$), 3.87 (3H, s, 4'-OC*H*$_3$); δ_C (151 MHz, Methanol-d$_4$) 180.5 (*C*-4), 164.9 (*C*-7), 163.2 (*C*-4'), 162.2 (*C*-5), 151.0 (*C*-2), 146.3 (*C*-9), 129.6 (*C*-2',6'), 127.0 (*C*-1'), 115.5 (*C*-3',5'), 111.2 (*C*-10), 109.1, (*C*-3), 96.5 (*C*-6), 92.6 (*C*-8), 56.2 (C-O*C*H$_3$), 56.1 (C-O*C*H$_3$), 56.0 (C-O*C*H$_3$); *m/z* (LC-MS, ES$^+$) 312 ([MH]$^+$), 645 ([M$_2$+Na]$^+$); HRMS (ASAP) found ([MH]$^+$) 312.1227; $C_{18}H_{18}NO_4$ requires M, 312.1236.

6.2.9 *2-(4'-Methoxyphenyl)-4,7-di-methoxyquinoline* (242)



Following the methylation procedure applied in **6.2.6**, a mixture of 2-(4'-methoxyphenyl)-7-methoxyquinoline-4-one **192B** (171.4 mg, 0.61 mmol), sodium hydride 60% (27.2 mg, 0.68 mmol) and methyl iodide (0.19 ml, 3.1 mmol) was heated at 100 ^{o}C in DMF (3 ml) for 2 h. Purification by chromatography (2: 4 EtOAc:hexane), afforded 2-(4'-methoxyphenyl)-4,7-di-methoxyquinoline **242** as a white solid (36 mg, 20 %), (mp = 108-109 ^{o}C); υ_{max} (ATR) 1595, 1507, 1453, 1361, 1332, 1252, 1224, 1207, 1172, 1149, 1110, 1021, 835, 814 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.1-8.0 (3H, m, 5-*H* & 2',6'-*H*), 7.4 (1H, d, *J* = 2.5 Hz, 8-*H*), 7.1 (1H, dd, *J* = 9.1 Hz, *J* = 2.5 Hz, 6-*H*), 7.1-7.0 (3H, m, 3-*H*, 3',5'-*H*), 4.1 (3H, s, 4'-C*H*$_3$), 4.0 (3H, s, 7-OC*H*$_3$), 3.9 (3H, s, 4-OC*H*$_3$); δ_C (176 MHz, $CDCl_3$) 162.9 (*C*-4'), 161.3 (*C*-7), 160.8 (*C*-4), 159.1 (*C*-2), 151.2 (*C*-9), 133.2 (*C*-1'), 128.9 (*C*-2',6'), 123.0 (*C*-5), 117.8 (*C*-6), 114.9 (*C*-10), 114.2 (*C*-3',5'), 107.5 (*C*-8), 96.3 (*C*-3), 55.7 (C-O*C*H$_3$), 55.6 (C-O*C*H$_3$), 55.5 (C-O*C*H$_3$); *m/z* (GC-MS, EI$^+$) 296 ([MH]$^+$, 18.5%), 295 ([M]$^+$, 100%), 294 ([M-H]$^+$, 66%), 280 ([M-CH$_3$]$^+$, 27%), 265 ([M-2CH$_3$]$^+$, 29%), 250 ([M-

$3CH_3]^+$, 13%), 235 ([MH-O-$3CH_3]^+$, 3%), 222 (3%); HRMS (ASAP) found ([MH]$^+$) 296.1276; $C_{18}H_{18}NO_3$ requires M, 296.1287.

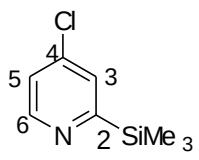
6.2.10 The preparation of 2-substituted pyridine derivatives

In a round bottomed flask, nBuLi was added dropwise with stirring at -5 ^{o}C to a solution of 2-methylaminoethanol in hexane. After 30 min stirring, the 4-substituted pyridine was then added with stirring for 1h. A solution of the appropriate electrophile in the stated solvent was then added dropwise at -78 ^{o}C. After stirring for 1.5 h, water was added to quench the reaction. The crude mixture was extracted with DCM (2 x 10 ml). The organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo.* Purification using chromatography on silica gel afforded the desired 2-substituted pyridine.

Protocol G1: nBuLi (2.5 ml, 4 mmol), 2-methylaminoethanol (0.2 ml, 2 mmol) in hexane (1.25 ml), 4-substituted pyridine (0.5 mmol) and the appropriate electrophile (2.5 mmol) in THF (5 ml).

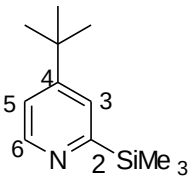
Protocol G2: nBuLi (2.5 ml, 4 mmol), 2-methylaminoethanol (0.2 ml, 2 mmol) in hexane (10 ml), 4-substituted pyridine (1 mmol) and the appropriate electrophile (2.5 mmol) in hexane (2.5 ml).

6.2.10.1 *4-Chloro-2-tri-methylsilylpyridine* (254)[140]



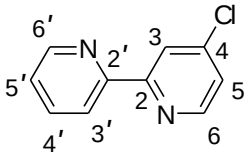
Following protocol **G1,** 4-chloropyridine **258** (56.7 mg) and TMSCl (317.5 µl) were combined to afford, following purification by chromatography (EtOAc:hexane: 1:8), 4-chloro-2-tri-methylsilylpyridine **254** as a white liquid (41 mg, 44%); υ_{max} (ATR) 1594, 1505, 1417, 1255, 1155, 1107, 851, 769 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.6 (1H, d, *J* = 5.3 Hz, 6-*H*), 7.5 (1H, d, *J* = 2.2 Hz, 3-*H*), 7.2 (1H, dd, *J* = 5.3 Hz, *J* = 2.2 Hz, 5-*H*), 0.3 (9H, s, C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 170.7 (*C*-2), 151.3 (*C*-6), 143.0 (*C*-4), 129.2 (*C*-3), 123.2 (*C*-5), -1.8 (Si*C*H_3); *m/z* (LC-MS, ES^+) 190 ([MH (^{30}Si,^{37}Cl)]$^+$, 30%), 189 ([MH (^{29}Si,^{37}Cl)]$^+$, 35%), 188 ([MH (^{28}Si,^{37}Cl)]$^+$, 100%), 187 ([M (^{30}Si,^{35}Cl)]$^+$, 67%), 186 ([M (^{29}Si,^{35}Cl)]$^+$, 30%), 185 ([M (^{28}Si,^{35}Cl)]$^+$, 95%).

6.2.10.2 *4-Tert-butyl-2-tri-methylsilylpyridine* (260)[141]



Following protocol **G1,** 4-tert-butylpyridine **249** (67.6 mg) and TMSCl (317.5 µl) were combined to afford, following purification by chromatography (EtOAc:hexane: 1:3), 4-tert-butyl-2-tri-methylsilylpyridine **260** as a white oil (35 mg, 17%); υ_{max} (ATR) 1598, 1409, 1273, 996, 842, 820, 569 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.7 (1H, d, *J* = 5.2 Hz, 6-*H*), 7.5 (1H, d, *J* = 2.7 Hz, 3-*H*), 7.2 (1H, dd, *J* = 5.2 Hz, *J* = 2.7 Hz, 5-*H*), 1.3 (9H, s, C*H*$_3$), 0.32 (9H, s, Si*CH*$_3$); δ_C (176 MHz, $CDCl_3$) 167.7 (*C*-2), 157.6 (*C*-4), 150.1 (*C*-6), 125.6 (*C*-3), 120.0 (*C*-5), 34.7 (4-*C*), 30.7 (4-C-(*C*H_3)$_3$), -1.6 (Si*C*H_3); *m/z* (LC-MS, ES^+) 210 ([MH (Si^{30})]$^+$, 30%), 209 ([MH (Si^{29})]$^+$, 32%), 208 ([MH (Si^{28})]$^+$, 100%).

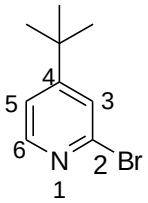
6.2.11 Preparation of *4-Chloro-2,2'-bipyridine* (255)[142] using Hiyama cross-coupling reaction [92]



Under N_2, in a closed microwave vessel, a solution of 2-bromopyridine **253** (79 mg, 0.5 mmol), 4-chloro-2-tri-methylsilanylpyridine **254** (185 mg, 1 mmol) in DMF (1.25 ml) and TBAF (2 mL of a 1M solution in THF, 2 mmol) were added to a stirred mixture of $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), PPh_3 (26 mg, 0.1 mmol) and CuI (188 mg, 1 mmol) in DMF (5ml). The reaction mixture was allowed to stir for 18 h. The reaction mixture was quenched by adding NH_4OH (5 ml), H_2O (5 ml), then filtered over a pad celite. The resulting mixture was extracted with Et_2O (2 x 20 ml). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification using chromatography on silica gel (hexane: EtOAc:Et_3N 8:2:0.1), afforded the 4-chloro-2,2´-bipyridine **255** as a white solid (52 mg, 54%). (m.p= 71.8-72.8 ^oC, lit.,[142] 71.4-72.2 ^oC); υ_{max} (ATR) 1575, 1551, 1453, 1390, 1281, 1087, 995, 835, 813, 786, 738, 726, 709, 618, 594, 478 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.7 (1H, m, 6'-*H*), 8.6 (1H, d, *J* = 5.3 Hz, 6-*H*), 8.5 (1H, s, 3-*H*), 8.4 (1H, d, *J* = 7.9 Hz, 3'-*H*), 7.83 (1H, t, *J* = 7.9 Hz, 4'-*H*), 7.36-7.31 (1H, m, 5'-*H*), 7.32 (1H, d, *J* = 5.3 Hz, 5-*H*); δ_C (176 MHz, $CDCl_3$) 157.7 (*C*-2), 154.9 (*C*-2'), 150.1 (*C*-6), 149.3 (*C*-6'), 145.4 (*C*-4), 137.2 (*C*-4'), 124.4 (*C*-5'), 124.0 (*C*-5), 121.7 (*C*-3), 121.5 (*C*-3'); *m/z* (LC-MS, EI^+) 193 ([MH (^{37}Cl)]$^+$, 35%), 191 ([MH (^{35}Cl)]$^+$, 35%).

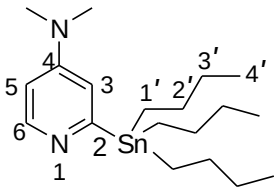
6.2.12 Preparation of 2,2'-bipyridine derivatives

6.2.12.1 *2-Bromo-4-tert-butylpyridine* (252)[141]



Following protocol **G2,** 4-tert-butylpyridine **249** (0.135 g) and CBr_4 (0.830 g) were combined to afford, following purification by chromatography (EtOAc:hexane: 1:9), 2-bromo-4-tert-butylpyridine **252** as an orange oil (112 mg, 52%); υ_{max} (ATR) 1585, 1530, 1476, 1378, 1265, 1144, 1085, 989, 854, 839, 756, 687, 618 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.24 (1H, d, *J* = 5.3 Hz, 6-*H*), 7.43 (1H, d, *J* = 1.7 Hz, 3-*H*), 7.21 (1H, dd, *J* = 5.3 Hz, *J* = 1.7 Hz, 5-*H*), 1.28 (9H, s, C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 163.4 (*C*-4), 150.0 (*C*-6), 142.7(*C*-2), 125.2 (*C*-3), 120.2 (*C*-5), 35.1 (4-*C*), 30.5 (4-C-(*C*H_3)$_3$); *m/z* (LC-MS, ES^+) 215 ([M (^{81}Br)]$^+$, 90%), 213 ([M (^{79}Br)]$^+$, 87%).

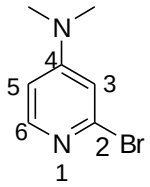
6.2.12.2 *4-Di-methylamino-2-tri-butylstannylpyridine* (266)[97]



Following protocol **G2,** 4-di-methylaminopyridine **247** (122 mg) and tri-butyltin chloride (0.7 ml) were reacted. Purification by chromatography (EtOAc:hexane:Et_3N 1:2:0.1) afforded the 4-di-methylamino-2-tri-butylstannylpyridine **266** as a yellow oil (0.25 g, 61%); υ_{max} (ATR) 1578, , 1534, 1490, 1464, 1444, 1365, 1275, 1215, 1070, 981, 959, 805, 663, 596, 505, 432 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.32 (1H, d, *J* = 6 Hz, 6-*H*), 6.7-6.6 (1H, d, $^3J^1_{H\text{-}^{119}Sn}$ = 2.9 Hz, 3-*H*), 6.34 (1H, dd, *J* = 6 Hz, *J* = 2.9 Hz, 5-*H*), 2.94 (6H, s, *N*-

CH_3), 1.55 (6H, m, 2'-*H*), 1.32 (6H, m, 3'-*H*), 1.1 (6H, m, 1'-*H*), 0.86 (9H, t, *J* =7.4 Hz, 4'-*H*); δ_C (176 MHz, $CDCl_3$) 172.1 (*C*-2, $^{1}J^{13}_{C\text{-}}{}^{119}_{Sn}$= 508.5 Hz), 152.1 (*C*-4, $^{3}J^{13}_{C\text{-}}{}^{119}_{Sn}$= 40.5 Hz), 150.1 (*C*-6, $^{3}J^{13}_{C\text{-}}{}^{119}_{Sn}$= 69.5 Hz), 115.5 (*C*-3, $^{2}J^{13}_{C\text{-}}{}^{119}_{Sn}$= 78.2 Hz), 105.5 (*C*-5), 38.9 (*N*-*C*H_3), 29.2 (*C*-2', $^{2}J^{13}_{C\text{-}}{}^{119}_{Sn}$= 20.1 Hz), 27.4 (*C*-3', $^{3}J^{13}_{C\text{-}}{}^{119}_{Sn}$= 55.5 Hz), 13.8 (*C*-4'), 9.7 (*C*-1', $^{1}J^{13}_{C\text{-}}{}^{119}_{Sn}$= 326.8 Hz); *m/z* (LC-MS, ES^+) 416 ([M (^{124}Sn)]$^+$), 414 ([M (^{122}Sn)]$^+$), 409 ([M (^{119}Sn)]$^+$).

6.2.12.3 *2-Bromo-4-di-methylaminopyridine* (267)[97,143]



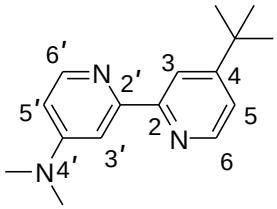
Following protocol **G2,** 4-di-methylaminopyridine **247** (122 mg) and CBr_4 (0.830 g) were reacted. Purification by chromatography (EtOAc:hexane: 1:1) afforded the 2-bromo-4-di-methylaminopyridine **267** as a yellow solid (90 mg, 45%), (mp = 55.5-57.0 ^{o}C); υ_{max} (ATR) 1591, 1516, 1440, 1383, 1266, 1223, 1130, 1069, 975, 808, 689, 444 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 7.9 (1H, d, *J* = 6 Hz, 6-*H*), 6.6 (1H, d, *J* = 2.4 Hz, 3-*H*), 6.4 (1H, dd, *J* = 6 Hz, *J* = 2.4 Hz, 5-*H*), 3.0 (6H, s, *N*-CH_3); δ_C (176 MHz, $CDCl_3$) 155.9 (*C*-4), 149.2 (*C*-6), 143.0 (*C*-2), 109.4 (*C*-3), 106.3 (*C*-5), 39.4 (*N*-*C*H_3); *m/z* (GC-MS, ES^+) 202 ([M (^{81}Br)]$^+$,97%), 200 ([M (^{79}Br)]$^+$, 100%), 121 ([M-(^{79}Br)]$^+$, 27%); HRMS (ES^+) found ([MH]$^+$) 201.0007, $C_7H_{10}{}^{79}BrN_2$ requires M, 201.0027.

6.2.12.4 Stille cross-coupling reaction to prepare bipyridine derivatives

6.2.12.4.1 Procedure H[99]

Under N_2, in a closed microwave vessel, 2-halo-4-substituted pyridine in DMF (2 ml) was added to a mixture of 4-di-methylamino-2-tri-butylstannylpyridine (0.1 g, 0.25 mmol) and $PdCl_2(PPh_3)_2$ (17.55 mg, 10 mol%, 0.025 mmol). The reaction mixture was heated at 110 ^oC for 18 h, H_2O (5 ml) was then added to the solution and the resulting mixture extracted with DCM (2 x 20 ml). The organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in DCM (10 ml) and then extracted by adding HCl (6M) (6 ml). Ammonium hydroxide 35% was then added to the aqueous solution to make the solution pH = 7-8. The crude mixture was extracted with DCM (2 x 20 ml). The organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo*. Purification using chromatography on silica gel (hexane: EtOAc: Et_3N 5:1:5) afforded the desired bipyridine product.

6.2.12.4.1.1 *4'-Di-methylamino-4-tert-butyl-2,2'-bipyridine* (250)



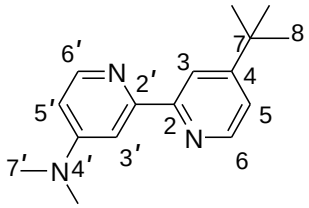
Following procedure **H in 6.2.12.4.1**, 2-chloro-4-tert-butylpyridine **265** (42.3 mg, 0.25 mmol), 4-di-methylamino-2-tri-butylstannylpyridine **266** and $PdCl_2(PPh_3)_2$ were reacted to afford 4'-di-methylamino-4-tert-butyl-2,2'-bipyridine **250** as a white solid (20.5 mg, 32%). (mp = 101.5-103 ^oC); υ_{max} (ATR) 1641, 1570, 1464, 1433, 1419, 1378, 1228, 1073, 998, 881, 851, 813, 800, 748, 588, 529 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.6 (1H, d, *J* = 5.2 Hz, 6-*H*), 8.45-8.43 (1H, m, 3-*H*), 8.3 (1H, d, *J* = 6.0 Hz, 6'-*H*), 7.68 (1H, d, *J* = 2.7 Hz, 3'-*H*),

7.29 (1H, dd, *J* = 5.2, *J* = 1.9 Hz, 5-*H*), 6.55(1H, dd, *J* = 6.0 Hz, *J* = 2.7 Hz, 5'-*H*), 3.11 (6H, s, *N*-C*H*$_3$), 1.38 (9H, s, 8-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 161.2 (*C*-4), 155.9 (*C*-2), 155.7 (*C*-4'), 149.0 (*C*-6), 148.4 (*C*-6'), 121.0 (*C*-5), 118.7 (*C*-3), 106.6 (*C*-5'), 104.3 (*C*-3'), 39.6 (*N*-*C*H$_3$), 35.2 (4-*C*), 30.8 (4-C-(*C*H$_3$)$_3$), unobserved (*C*-2'); *m/z* (GC-MS, EI$^+$) 256 ([MH]$^+$, 11%) , 255 ([M]$^+$, 67%), 241 ([MH-CH$_3$]$^+$, 17%), 240 ([M-CH$_3$]$^+$, 100%), 224 found, 212 ([MH-*N*(CH$_3$)$_2$]$^+$, 25%); HRMS (ES$^+$) found ([MH]$^+$) 256.1812, $C_{16}H_{22}N_3$ requires M, 256.1814.

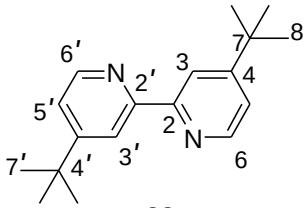
6.2.12.4.2 Procedure I:[97]

6.2.12.4.2.1 *4'-Di-methylamino-4-tert-butyl-2,2'-bipyridine* (250)

6.2.12.4.2.2 *4,4'-Di-tert-butyl-2,2'-bipyridine* (22)



250



22

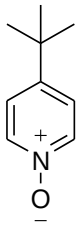
Under N_2, in a round bottomed flask fitted with a condenser, 2-bromo-4-tert-butylpyridine **252** (0.118g, 0.55 mmol), 4-di-methylamino-2-tri-butylstannylpyridine **266** (0.205g, 0.5 mmol), $PdCl_2(PPh_3)_2$ (19 mg, 0.027 mmol) and PPh_3 (0.014, 0.055 mmol) in xylene (10 ml) were heated at 130 ^oC for 24 h. The crude mixture was filtered through celite and then extracted with DCM (2 x 20 ml). The organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo*. Purification using chromatography on silica gel (hexane:EtOAc:Et_3N 5:1:5), afforded 4'-di-methylamino-4-tert-butyl-2,2'-bipyridine **250** as a brown solid (44.6 gm, 32%); Data have been identified above in **6.2.12.4.1.1**.

Furthermore**,** 4,4'-di-tert-butyl-2,2'-bipyridine **22** was isolated as a white solid (21 mg, 14%).

6.2.13 Preparation of *6-chloro-2,2'-bipyridine derivatives*

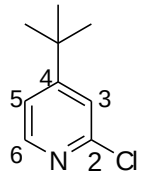
6.2.13.1 Preparation of 2,6-di-chloro-4-substitutedpyridine:

6.2.13.1.1 *4-Tert-butylpyridine-N-oxide* (270)[98]



A mixture of 4-tert-butylpyridine **249** (4 ml, 27.3 mmol), H_2O_2 (22 ml, 35% 255 mmol) and glacial acetic acid (30 ml) was refluxed at 80 ^oC for 4 h. Another 22 ml of H_2O_2 was then added to the mixture of reaction. After refluxing overnight, 50 ml of solvent was removed *in vacuo*. H_2O (5.5 ml) was then added and removed as well *in vacuo*. NaOH (6%) was then added to make the solution base (pH = 9, pH paper). The crude mixture was then extracted with DCM (2 x 20 ml). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford 4-tert-butylpyridine-*N*-oxide **270** (3.8 g), which was used directly in the next step without further purification.

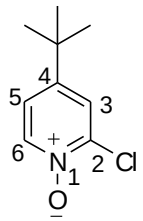
6.2.13.1.2 *2-Chloro-4-tert-butylpyridine* (265)[98]



Under argon, pyridine-*N*-oxide **270** (3.8 g) and $POCl_3$ (15.5 ml, 166.3 mmol) were combined and heated at 105 ^oC for 20 h. After cooling to room temperature, the $POCl_3$

was removed *in vacuo*. $NaHCO_3$ solution was then added to neutralise the solution (pH = 7). The crude mixture was then extracted with ether (2 x 20 ml). The organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo*. Purification using chromatography on silica gel (1:9) (EtOAc:hexane) afforded 2-chloro-4-tert-butylpyridine **265** as a yellow oil (2.1 g, 45%); υ_{max} (ATR) 1590, 1534, 1476, 1380, 1267, 1150, 1092, 992, 864, 840, 773, 694, 628 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.2 (1H, d, *J* = 5.3 Hz, 6-*H*), 7.24 (1H, d, *J* = 1.7 Hz, 3-*H*), 7.14 (1H, dd, *J* = 5.3 Hz, *J* = 1.7 Hz, 5-*H*), 1.24 (9H, s, C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 163.5 (*C*-4), 151.7 (*C*-2), 149.4 (*C*-6), 121.0 (*C*-3), 119.7 (*C*-5), 35.0 (4-*C*), 30.4 (4-C-(*C*H_3)$_3$); *m/z* (GC-MS, EI^+) 171 ([M (^{37}Cl)]$^+$, 14%), 169 ([M (^{35}Cl)]$^+$, 44%), 156 ([M (^{37}Cl)-CH_3]$^+$, 37%), 154 ([M (^{35}Cl)-CH_3]$^+$, 100%).

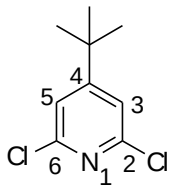
6.2.13.1.3 *2-Chloro-4-tert-butylpyridine-N*-oxide (274)[98]



Following the protocol described above in **6.2.13.1.1**, 2-chloro-4-tert-butylpyridine **265** (416 mg, 2.46 mmol) was oxidized with H_2O_2 to afford, without further purification, 2-chloro-4-tert-butylpyridine-*N*-oxide **274** as a brown solid (0.38 g, 83%), (mp = 125-126.5 ^oC); υ_{max} (ATR) 3026, 2957, 1717, 1613, 1524, 1476, 1405, 1365, 1249, 1157, 1081, 891, 830, 822, 750, 678, 614 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.3 (1H, d, *J* = 6.9 Hz, 6-*H*), 7.44 (1H, d, *J* = 2.7 Hz, 3-*H*), 7.18 (1H, dd, *J* = 6.9 Hz, *J* = 2.7 Hz, 5-*H*), 1.30 (9H, s, C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 151.415 (*C*-4), 141.4 (*C*-2), 139.9 (*C*-6), 124.2 (*C*-3), 121.5 (*C*-

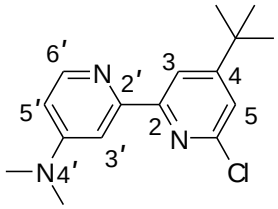
5), 34.8 (4-*C*), 30.5 (4-C-(*C*H_3)$_3$); *m/z* (LC-MS, ES$^+$) 188 ([MH (^{37}Cl)]$^+$, 37%), 186 ([MH (^{35}Cl)]$^+$, 100%).

6.2.13.1.4 *2,6-Di-chloro-4-tert-butylpyridine* (276)[98]



Following the protocol described above in **6.2.13.1.2**, 2-chloro-4-tert-butylpyridine-*N*-oxide **274** (0.34 g, 1.83 mmol) was reacted with $POCl_3$ (1.1 ml, 11.8 mmol) to afford, following purification using chromatography on silica gel (0.5:9.5) (EtOAc:hexane) 2,6-di-chloro-4-tert-butylpyridine **276** as a white crystal solid (0.26 g, 70%), (mp 82.5-84 ^{o}C); υ_{max} (ATR) 2968, 2870, 1581, 1531, 1479, 1368, 1360, 1263, 1250, 1171, 1101, 990, 879, 861, 807, 772, 633 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 7.18 (2H, s, 3,5-*H*), 1.24 (9H, s, C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 166.5 (*C*-4), 150.7 (*C*-2,6), 120.4 (*C*-3,5), 35.6 (4-*C*), 30.5 (*C*H_3); *m/z* (GC-MS, EI$^+$) 207 ([M (^{37}Cl,^{37}Cl)]$^+$, 4%), 205 ([M (^{35}Cl,^{37}Cl)]$^+$, 23%), 203 ([M (^{35}Cl,^{35}Cl)]$^+$, 36%), 192 ([M (^{37}Cl,^{37}Cl)-CH_3]$^+$, 10%), 190 ([M (^{35}Cl,^{37}Cl)-CH_3]$^+$, 63%), 188 ([M (^{35}Cl,^{35}Cl)-CH_3]$^+$, 100%).

6.2.13.2 *4'-Di-methylamino-4-tert-butyl-6-chloro-2,2'-bipyridine* (277)



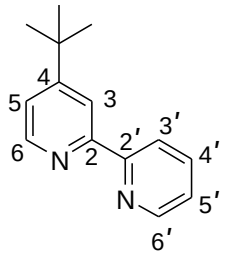
Following procedure **H** in **6.2.12.4.1**, 2,6-di-chloro-4-tetr-butylpyridine **276** (51 mg, 0.25 mmol), 4-di-methylamino-2-tri-butylstannylpyridine **266** and $PdCl_2(PPh_3)_2$ were

reacted to afford, 4'-di-methylamino-4-tert-butyl-6-chloro-2,2'-bipyridine **277** as a yellow solid (22.4 mg, 31%), (mp = 239.5-240.5 °C); υ_{max} (ATR) 1582, 1538, 1379, 1300, 1160, 990, 889, 853, 800, 776, 750, 675, 621, 558, 469, 448 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.4 (1H, s, 3-*H*), 8.3 (1H, d, *J* = 6.0 Hz, 6'-*H*) 7.66 (1H, d, *J* = 2.7 Hz, 3'-*H*), 7.3 (1H, d, *J* = 1.6 Hz, 5-*H*), 6.5 (1H, dd, *J* = 6.0 Hz, *J* = 2.7 Hz, 5'-*H*), 3.11 (6H, s, *N*-CH_3), 1.38 (9H, s, 8-CH_3); δ_C (176 MHz, $CDCl_3$) 164.5 (*C*-4), 155.5 (*C*-4'), 151.0 (*C*-6), 148.8 (*C*-6'), 121.2 (*C*-5), 117.4 (*C*-3), 106.9 (*C*-5'), 104.6 (*C*-3'), 39.5 (*N*-*C*H_3), 35.5 (4-*C*), 30.7 (4-C-(*C*H_3)$_3$), unobserved (*C*-2'), (*C*-2); *m/z* (GC-MS, EI^+) 291 ([M (^{37}Cl)]$^+$, 21%), 289 ([M (^{35}Cl)]$^+$, 63%), 276 ([M (^{37}Cl)-CH_3]$^+$, 31%)**,** 274 ([M (^{35}Cl)-CH_3]$^+$, 100%), 258 found, 246 ([MH (^{35}Cl)-*N*(CH_3)$_2$]$^+$, 31%)**,** 233 found; HRMS (ES^+) found ([MH]$^+$) 290.1431, $C_{16}H_{21}{}^{35}ClN_3$ requires M, 290.1424.

6.2.14 Preparation of 2,2'-bipyridine derivatives using copper and lithium salts

6.2.14.1 Procedure J:[101]

6.2.14.1.1 *4-Tert-butyl-2,2'*-bipyridine (281)[144]



Under N_2, in a closed microwave vessel, a mixture of 2-bromo-4-tert-butylpyridine **252** (64.2 mg, 0.3 mmol), 2-tri-butylstannylpyridine **272** (80%, 156 mg, 0.36 mmol), $PdCl_2(PPh_3)_2$ (3.75 mol%, 0.011 mmol) and LiCl (93.1 mg, 2.2 mmol) in toluene (3 ml)

were heated at 120 ^{o}C for 48 h. H_2O (5 ml) was then added to the solution, and the crude mixture extracted with DCM (2 x 20 ml). The organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in DCM (10 ml) and then extracted by adding HCl (6M) (6 ml). Ammonium hydroxide 35% was then added to the aqueous solution to make the solution pH = 7-8. The crude mixture was extracted with DCM (2 X 20 ml). The organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo*. Purification using reversed phase chromatography (C-18 SiO_2), afforded 4-tert-butyl-2,2'-bipyridinyl **281** as an orange oil (26 mg, 40%); υ_{max} (ATR) 1600, 1584, 1546, 1458, 1391, 1257, 1072, 992, 866, 792, 743, 648, 618 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.69 (1H, m, 6'-*H*) 8.59 (1H, d, *J* = 5.7 Hz, 6-*H*), 8.42 (1H, s, 3-*H*), 8.38 (1H, d, *J* = 8.0 Hz, 3'-*H*), 7.81 (1H, t, *J* = 8.0 Hz, 4'-*H*), 7.36-7.28 (2H, m, 5,5'-*H*), 1.39 (9H, s, 4-(C*H*$_3$)$_3$); δ_C (176 MHz, $CDCl_3$) 161.2 (*C*-4), 156.7 (*C*-2'), 156.1 (*C*-2), 149.2 (*C*-6',6), 137.0 (*C*-4'), 123.7 (*C*-5'), 121.5 (*C*-3'), 121.1 (*C*-5), 118.3 (*C*-3), 35.2 (4-*C*), 30.7 (4-C-(*C*H$_3$)$_3$); *m/z* (LC-MS, ES$^+$) 447 ([M$_2$+ Na]$^+$, 57%), 213 ([MH]$^+$, 100%).

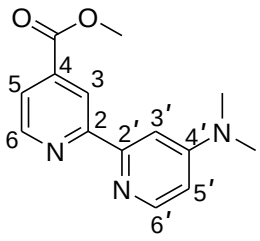
6.2.14.2 Procedure K[102]

Under N_2, a mixture of 4-di-methylamino-2-tri-butylstannylpyridine **266** (0.83 g, 2 mmol), 2-halo-4-substituted pyridine (2 mmol), $Pd(PPh_3)_4$ (0.12 g, 0.1 mmol, 5 mol%) and CuBr (0.02 g, 0.14 mmol, 7 mol%) in dry dioxane (15 ml) were refluxed at 101 ^{o}C for 17 h. The reaction mixture was then cooled and concentrated *in* vacuo. The crude mixture was then dissolved from DCM and washed by water three times. The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo* to afford, following

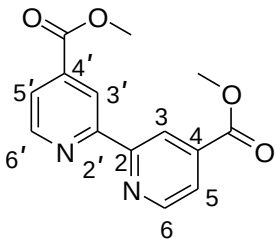
trituration with hexane to remove tri-butyltin chloride, chromatography in aluminum dioxide (PH= 7), the desired bipyridine product.

6.2.14.2.1 *4'-Di-methylamino-4-carboxylic acid methyl ester-2,2'-bipyridine* (285)

6.2.14.2.2 *4,4'-Di-carboxylic acid methyl ester-2,2'-bipyridine* (286)



285

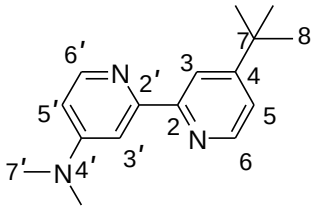


286

Following procedure **K** in **6.2.14.2**, methyl-2-bromo or chloroisonicotinate **284**, **151** (2 mmol) and 4-di-methylamino-2-tri-butylstannylpyridine **266** were coupled to afford, following chromatography (EtOAc:hexane 3:7), 4'-di-methylamino-4-carboxylic acid methyl ester-2,2'-bipyridine **285** as an off white solid (265 mg, 50%), (mp = 145.5-146.5 ^{o}C); υ_{max} (ATR) 2925, 1716, 1592, 1544, 1510, 1470, 1435, 1374, 1286, 1228, 1102, 980, 858, 798, 768, 739 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.92-8.89 (1H, s, 3-*H*), 8.79 (1H, d, *J* = 4.9 Hz, 6-*H*), 8.34 (1H, d, *J* = 5.8 Hz, 6'-*H*), 7.83 (1H, dd, *J* = 4.9 Hz, *J* = 1.6 Hz, 5-*H*), 7.71 (1H, d, *J* = 2.7 Hz, 3'-*H*), 6.55 (1H, dd, *J = 5.8 Hz, J* = 2.7 Hz, 5'-*H*), 3.96 (3H, s, OC*H*$_3$), 3.1 (6H, s, *N*-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 166.0 (*C*=O), 158.3 (*C*-2), 155.5 (*C*-2'), 155.4 (*C*-4'), 149.7 (*C*-6), 149.6 (*C*-6'), 138.4 (*C*-4), 122.6 (*C*-5), 120.7 (*C*-3), 107.1 (*C*-5'), 104.1 (*C*-3'), 52.7 (O*C*H$_3$), 39.5 (*N*-*C*H$_3$); m/z (GC-MS, EI$^+$) 257 ([M]$^+$, 77%), 242 ([M-CH$_3$]$^+$, 100%), 214 found, 199 ([MH-COOMe]$^+$, 41%); *m/z* (LC-MS, ES$^+$) 257 ([M]$^+$), 258 ([MH]$^+$); HRMS (ES$^+$) found ([MH]$^+$) 258.1243, $C_{14}H_{16}N_3O_2$ requires M, 258.1243.

Furthermore**,** 4,4'-di-carboxylic acid methyl ester-2,2'-bipyridine **286** was isolated as a white solid (0.01g, 2%), (mp = 207.3-208.5 ^{o}C); υ_{max} (ATR) 1728 (C=O), 1590, 1557, 1433, 1358, 1290, 1244, 1123, 957, 757, 722, 696, 668, 401 δ_H (700 MHz, $CDCl_3$) 8.96-8.90 (2H, m, 3, 3'-*H*), 8.86 (2H, d, *J* = 5 Hz, 6, 6'-*H*), 7.9 (2H, dd, *J* = 5 Hz, *J* = 1.6 Hz, 5,5'-*H*), 4.0 (6H, s, (OCH_3)$_2$); δ_C (176 MHz, $CDCl_3$) 165.76 (*C*=O), 156.64 (*C*-2), 150.28 (*C*-6), 138.74 (*C*-4), 123.4 (*C*-5), 120.7 (*C*-3), 52.9 (OCH_3); *m/z* (LC-MS, ES^+) 273 ($[MH]^+$).

6.2.14.2.3 *4'-Di-methylamino-4-tert-butyl-2,2'-bipyridine* (250)



Following procedure **K** in **6.2.14.2**, 2-bromo-4-tert-butylpyridine **252** (0.43 g, 2 mmol) and 4-di-methylamino-2-tri-butylstannylpyridine **266** were coupled to afford, following chromatography (EtOAc:hexane 2:8), 4'-Di-methylamino-4-tert-butyl-2,2'-bipyridine **250** as a white solid (240 mg, 47%). Data have been identified above in **6.2.12.4.1.1**.

6.2.15 Evaluation of ligands in the borylation of aromatic compounds

6.2.15.1 Evaluation of ligands using anisole in the borylation reaction:

$[Ir(OMe)cod]_2$ (0.01 g, 0.015 mmol, 1.5 mol %), ligand (3 mol %) and B_2pin_2 (254 mg, 1.0 mmol) were added to a (5 ml) microwave vessel. The vessel was evacuated, backfilled with N_2 and THF (2 ml) was then added. Anisole **35** (109 µl, 1.0 mmol) was added and the reaction mixture was carried out at r.t for the stated period before being quenched by the addition of DCM (2 ml). The reaction mixture was then

concentrated *in vacuo* to afford the crude product, which confirmed by GC MS and H NMR analysis.

6.2.15.2 Evaluation of ligands using m-xylene in the borylation reaction:

$[Ir(OMe)cod]_2$ (0.01 g, 0.015 mmol, 1.5 mol %), ligand (3 mol %) and B_2pin_2 (305 mg, 1.2 mmol) were added to a (5 ml) microwave vessel. The vessel was evacuated, backfilled with N_2. THF (2 ml) was added, and then m-xylene **19** (0.124 ml, 1.0 mmol) added. The microwave vessel was vigorously shaken and 0.5 ml of reaction mixture was then transferred to a Young's Tap-sealed NMR tub containing a coaxial tub filled with acetone-d_6. The reaction was heated and monitored at the stated temperature for the stated period by ^{1}H NMR spectrum.

6.2.15.3 Evaluation of ligands using methyl-2-methoxybenzoate in the borylation reaction:

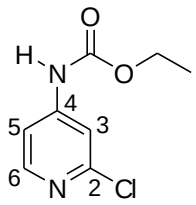
$[Ir(OMe)cod]_2$ (0.01 g, 0.015 mmole, 1.5 mol %), ligand (3 mol %) and B_2pin_2 (305 mg, 1.2 mmol) and methyl-2-methoxybenzoate **57** (166 mg, 1.0 mmol) were added to a (5 ml) microwave vessel. The vessel was evacuated, backfilled with N_2. THF (2 ml) was then added. This reaction was carried out at r.t for the stated period before being quenched by the addition of DCM (2 ml). The reaction mixture was then concentrated *in vacuo* to afford the crude product, which confirmed by GC MS and H NMR analysis.

6.2.16 Preparation of 4, 4'-di-substituted-2,2'-bipyridine derivatives

6.2.16.1 Preparation of carbamate derivatives, Procedure L

In round bottom flask, acyl chloride (12.0 mmol) was added dropwise to a stirred solution of the amine derivative (8.0 mmol) and tri-ethylamine (1.12 ml, 8.0 mmol) in dry DCM (35 ml) at 0 ^{o}C. The reaction was allowed to warm-up slowly to room temperature and then stirred for further 17 h. The crude mixture was then washed with saturated aq. $NaHCO_3$ until the aqueous washings were neutral. The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product.

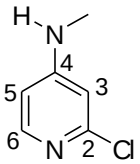
6.2.16.1.1 *(2-Chloro-pyridin-4-yl)-carbamic acid ethyl ester* (292)



Following procedure **L**, ethyl chloroformate (1.2 ml, 12 mmol) and 2-chloro-4-aminopyridine **291** (8 mmol, 1.0 g) were combined to afford, without further purification, (2-chloro-pyridin-4-yl)-carbamic acid ethyl ester **292** as a white solid (1.5 g, 96%), (mp = 136.8-137.8 ^{o}C); υ_{max} (ATR) 1739 (C=O), 1604, 1584, 1509, 1438, 1474, 1391, 1315, 1279, 1273, 1240, 1214, 1131, 1080, 1064, 1007, 990, 937, 866, 830, 608, 450 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.2 (1H, d, *J* = 5.7 Hz, 6-*H*), 7.6 (1H, s, *NH*) 7.5 (1H, d, *J* = 2 Hz, 3-*H*), 7.3 (1H, dd, *J* = 5.7 Hz, *J* = 2 Hz, 5-*H*), 4.2 (2H, q, *J* = 7.1 Hz, CH_2), 1.3 (3H, t, *J* = 7.1 Hz, CH_3); δ_C (176 MHz, $CDCl_3$) 153.0 (C=O), 152.0 (*C*-2), 150.0 (*C*-6), 148.0(*C*-4), 112.4 (*C*-3), 112.0 (*C*-5), 62.2 (*C*H_2), 14.5 (*C*H_3); *m/z* (GC-MS, EI^{+}) 202 ([M (^{37}Cl)]$^{+}$, 35%),

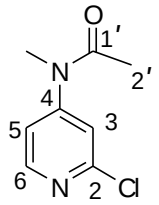
200 ([M (^{35}Cl)]$^+$, 100%), 156 ([M (^{37}Cl)-C_2H_6O]$^+$, 26%), 154 ([M (^{35}Cl)-C_2H_5O]$^+$, 79%), 143 & 141 found, 130 ([MH (^{37}Cl)-$C_3H_5O_2$]$^+$, 23%), 128 ([MH (^{35}Cl)-$C_3H_5O_2$]$^+$, 66%), 119 ([M-(^{35}Cl) C_2H_6O]$^+$, 53%); HRMS (ES$^+$) found ([MH]$^+$) 201.0422, $C_8H_{10}{}^{35}ClN_2O_2$ requires M, 201.0431.

6.2.16.2 *2-Chloro-4-(N-methylamino)-pyridine* (293)



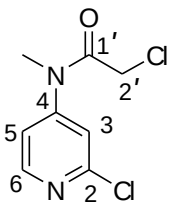
Under N_2, in a 50 ml round bottomed flasks, $LiAlH_4$ (2.5 ml of a 2.4 M solution in THF, 6.0 mmol) was added dropwise to a stirred solution of (2-chloro-pyridin-4-yl)-carbamic acid ethyl ester **292** (1.0 g, 5.0 mmol) in dry THF (20 ml) at 0 ^{o}C. The reaction was then allowed to stir at room temperature for 17 h and then quenched by the dropwise addition of H_2O (0.23 ml), 15% NaOH (0.23 ml) and H_2O (0.7 ml). The mixture was then filtered through celite and the solid phase was washed with THF. The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo* to afford, following chromatography (EtOAc:hexane 1:1), 2-chloro-4-(*N*-methylamino)-pyridine **293** as a white solid (0.54 g, 76%), (mp = 73.9-74.9 ^{o}C); υ_{max} (ATR) 3244 (*N*H), 1592, 1464, 1429, 1356, 1264, 1256, 1120, 1070, 980, 867, 834, 811, 717, 613, 443 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 7.9 (1H, d, *J* = 5.8 Hz, 6-*H*), 6.4 (1H, d, *J* = 2.2 Hz, 3-*H*), 6.3 (1H, dd, *J* = 5.8 Hz, *J* = 2.2 Hz, 5-*H*), 4.9 (1H, bs, *NH*), 2.8 (3H, d, *J* = 4.8 *Hz, CH$_3$*); δ_C (176 MHz, $CDCl_3$) 156.4 (*C*-4), 152.1 (*C*-2), 149.0 (*C*-6), 107.1 (*C*-5), 105.7 (*C*-3), 29.4 (*C*H_3); *m/z* (GC-MS, EI$^+$) 144 ([M (^{37}Cl)]$^+$, 34%), 142 ([M (^{35}Cl)]$^+$, 100%). HRMS (ES$^+$) found ([MH]$^+$) 143.0355, $C_6H_8{}^{35}ClN_2$ requires M, 143.0376.

6.2.16.3 *N-(2-Chloropyridin-4-yl)-N-methylacetamide* (294)



Following procedure **L**, 2-chloro-4-(*N*-methylamino)-pyridine **293** (1.14 g, 8.0 mmol) and acetyl chloride (0.85 ml, 12.0 mmol) were combined to afford, following chromatography ($CHCl_3$:EtOAc 2.0:1.0), *N*-(2-chloropyridin-4-yl)-*N*-methylacetamide **294** as a white solid (0.62g, 42%), (mp = 62.5-63.5 ^oC); υ_{max} (ATR), 1652 (C=O), 1582, 1549, 1471, 1425, 1379, 1360, 1301, 1082, 992, 982, 946, 858, 782, 734, 618, 596, 486, 446, 437, cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.3 (1H, d, *J* = 5.5 Hz, 6-*H*), 7.2 (1H, d, *J* = 2.0 Hz, 3-*H*), 7.1 (1H, dd, *J* = 5.5 Hz, *J* = 2.0 Hz, 5-*H*), 3.25 (3H, s, *N*-C*H*$_3$), 3.05 (3H, s, 2'-*H*), δ_C (176 MHz, $CDCl_3$) 169.8 (*C*-1'), 153.3 (*C*-4), 152.27 (*C*-2), 150.4 (*C*-6), 120.5 (*C*-3), 119.1 (*C*-5), 36.8 (C-*N*-*C*H_3), 22.9 (*C*-2'); *m/z* (LC-MS, ES^+) 185 ([MH (^{35}Cl)]$^+$, 100%), 187 ([MH (^{37}Cl)]$^+$, 30%); *m/z* (GC-MS, EI^+) 186 ([M (^{37}Cl)]$^+$, 8%), 184 ([M (^{35}Cl)]$^+$, 25%), 144 ([MH (^{37}Cl)-C_2H_3O]$^+$, 34%), 142 ([MH (^{35}Cl)-C_2H_3O]$^+$, 100%). HRMS (ES^+) found ([MH]$^+$) 185.0486, $C_8H_{10}{}^{35}ClN_2O$ requires M, 185.0482.

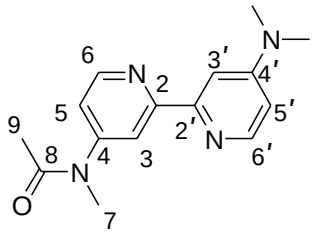
6.2.16.4 *2-Chloro-N-(2-chloropyridin-4-yl)-N-methylacetamide* (295)



Following procedure **L**, 2-chloro-4-(*N*-methylamino)-pyridine **293** (1.14 g, 8.0 mmol) and 2-chloroacetylchloride (0.96 ml, 12.0 mmol) were combined to afford, following chromatography (MeOH:DCM 1.0:20), 2-chloro-*N*-(2-chloropyridin-4-yl)-*N*-methyl-

acetamide **295** as an off white solid (1.58 g, 90%), (mp = 86.5-87.5 ^{o}C); υ_{max} (ATR) 1677 (C=O), 1581, 1549, 1467, 1367, 1259, 1117, 1084, 1046, 991, 943, 801, 785, 734, 712, 652, 639, 562, 479, 431 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.44 (1H, d, *J* = 5.4 Hz, 6-*H*), 7.31 (1H, d, *J* = 1.9 Hz, 3-*H*), 7.21 (1H, dd, *J* = 5.4 Hz, *J* = 1.9 Hz, 5-*H*), 4.03 (2H, s, 2'-*H*), 3.37 (3H, s, *N*-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 166.0 (*C*-1'), 153.0 (*C*-2), 152.4 (*C*-4), 151.1 (*C*-6), 121.0 (*C*-3), 119.4 (*C*-5), 41.4 (*C*-2'), 37.5 (*C*H$_3$); *m/z* (GC-MS, EI$^+$) 222 ([M (^{37}Cl,^{37}Cl)]$^+$, 6%), 220 ([M (^{35}Cl,^{37}Cl)]$^+$, 35%), 218 ([M (^{35}Cl,^{35}Cl)]$^+$, 54%), 185 ([M (^{37}Cl)-(^{37}Cl)]$^+$, 8%), 183 ([M (^{35}Cl)-(^{35}Cl)]$^+$, 27%), 171 ([M (^{37}Cl)-(^{37}Cl)-CH_2]$^+$, 31%), 169 ([M (^{35}Cl)-(^{35}Cl)-CH_2]$^+$, 100%), 144 ([MH (^{37}Cl)-(^{37}Cl)-C_2H_2O]$^+$, 25%), 142 ([MH (^{35}Cl)-(^{35}Cl)-C_2H_2O]$^+$, 81%); HRMS (ES$^+$) found ([MH]$^+$) 219.0079, $C_8H_9{}^{35}Cl_2N_2O$ requires M, 219.0092.

6.2.16.5 *2-(4'-Di-methylamino-2,2'-bipyridine-4-yl)-N-methylacetamide* (296)



Following procedure **K** in **6.2.14.2**, *N*-(2-chloropyridin-4-yl)-*N*-methylacetamide **294** (0.37 g, 2 mmol) and 4-di-methylamino-2-tri-butylstannylpyridine **266** were coupled to afford, following chromatography (MeOH:DCM 1:40), 2-(4′-di-methylamino-2,2′-bipyridine-4-yl)-*N*-methylacetamide) **296** as an off white solid (27 mg, 5%), (mp = 122.5-123.5 ^{o}C); υ_{max} (ATR) 1666 (C=O), 1576, 1473, 1463, 1375, 1334, 1252, 1223, 1146, 988, 829, 750, 611, 554 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.68 (0.1H, d, *J* = 5.2 Hz, 6-*H*, rotamer A), 8.65 (0.9H, d, *J* = 5.2 Hz, 6-*H*, rotamer B), 8.32 (1H, m, 3-*H*), 8.29 (1H, d, *J* = 6.0 Hz, 6'-*H*), 7.72 (1H, d, *J* = 2.7 Hz, 3'-*H*), 7.24-7.4 (1H, m, 5-*H* rotamers A and B), 6.56

(1H, dd, *J* = 6.0 Hz, *J* = 2.7 Hz, 5'-*H*), 3.37 (3H, s, *N*C*H*$_3$), 3.12 (6H, s, *N*-(C*H*$_3$)$_2$), 2.09-2.07 (3 H, s, C*H*$_3$, rotamers A and B); δ_C (176 MHz, $CDCl_3$) 170.1 (*C*=O), 155.7 (*C*-4'), 155.0 (*C*-2'), 152.7 (*C*-4), 150.7 (*C*-6, rotamer A), 150.3 (*C*-6, rotamer B), 121.4 (*C*-5, rotamer A), 121.1 (*C*-5, rotamer B), 118.4 (*C*-3), 107.1 (*C*-5'), 104.2 (*C*-3'), 39.6 (*N*-(*C*H_3)$_2$), 37.0 (*NC*H_3), 22.9 (*C*H_3, rotamer A and B), unobserved (C-2, C-6'); *m/z* (LC-MS, EI^+) 271 ($[MH]^+$). HRMS (ES^+) found ($[MH]^+$) 271.1554, $C_{15}H_{19}N_4O$ requires M, 271.1559.

6.2.17 The borylation of pyridine derivatives

$[Ir(OMe)cod]_2$ (X mmol, X mol %), dtbpy (2X mmol, 2X mol%), B_2pin_2 (X mmol) and the substrate (1.0 mmol).

Protocol M1: All reagents above except the substrate were placed in the reaction vessel which was then sealed, evacuated, backfilled with N_2 and the stated solvent was then added. The substrate was placed in a second vessel, sealed, evacuated, backfilled with N_2, dissolved in the stated solvent and transferred to vessel 1 using a syringe.

Protocol M2: All reagents above were placed in the reaction vessel which was then sealed, evacuated, backfilled with N_2 and MTBE (2 ml) was then added.

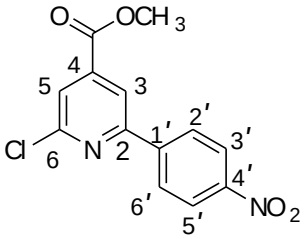
Protocol M3: All reagents above except the substrate were placed in the reaction vessel which was then sealed, evacuated, backfilled with N_2 and MTBE (2 ml) was then added. The substrate was added using a syringe.

All the reaction mixtures above were heated in μW reactor at the stated temperature for the stated period. After cooling, the reaction mixture was concentrated *in vacuo* to afford the crude borylated product. Where relevant, this crude borylated product was used in the Suzuki-Miyaura cross-coupling reaction, without further purification.

6.2.18 General procedure N: Susuki Miyaura-cross coupling

Following borylation using protocol **M1 or M2**, a mixture of Ar-Bpin (1.0 mmol), aryl halide (1.5 or 1.1 mmol), $PdCl_2$(dppf) (5 mol%) and Cs_2CO_3 (0.65 g, 2.0 mmol) were placed in dry microwave vessel (5 ml) while was then evacuated and backfilled with N_2. DMA (2 ml) was then added. The reaction mixture was heated in microwave reactor at the stated temperature for the stated period. After cooling, the reaction mixture was concentrated *in vacuo* then re-dissolved by EtOAc (40 ml) and wash with $NaHCO_3$ (aq.) to afford, following chromatography the desired product.

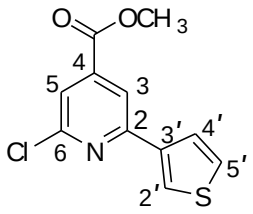
6.2.18.1 *Methyl-6-chloro-2-(4'-nitrophenyl)-pyridine-4-carboxylate* (310)



Methyl-2-chloroisonicotinate **151** (171.5 mg, 1.0 mmol) in MTBE (1.0 ml) was borylated following standard protocol **M1** [[Ir(OMe)cod]$_2$ (33.15 mg, 0.05 mmol, 5 mol%), dtbpy (10 mol%, 26.8 mg) and B_2pin_2 (1.2 mmol, 305 mg) in MTBE (1.5 ml), reaction time= 30 min, reaction temperature= 120 ^oC]. The crude boronate ester (~1.0 mmol) was directly used in Suzuki Miyaura coupling following general procedure **N** with 4-iodonitrobenzene (374 mg, 1.5 mmol) at 100 ^oC for 3 h to afford, following chromatography (DCM:toluene 3:7), Methyl-6-chloro-2-(4'-nitrophenyl)-pyridine-4-carboxylate **310** as a yellow solid (130 mg, 45 %), (mp = 165.5-166 ^oC); υ_{max} (ATR) 1733 (C=O), 1591, 1557, 1514, 1439, 1404, 1340, 1317, 1252, 1244, 1156, 1104, 982, 857, 818, 770, 755, 742, 722, 689 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.36-8.33 (2H, m, 3',5'-*H*), 8.3 (1H, d, *J* = 1.1 Hz, 3-*H*), 8.3-8.23 (2H, m, 2',6'-*H*), 7.9 (1H, d, *J* = 1.1 Hz, 5-*H*), 4.0 (3H, s,

OCH_3); δ_C (176 MHz, $CDCl_3$) 164.3 (*C*=O),156.9 (*C*-2), 152.9 (*C*-6), 149.0 (*C*-4'), 142.8 (*C*-1'), 141.5 (*C*-4), 128.1 (*C*-2',6'), 124.3 (*C*-3',5'), 123.8 (*C*-3), 119.0 (*C*-5), 53.4 (*O*-*C*H_3); *m/z* (GC-MS, EI^+) 294 ([M (^{37}Cl)]$^+$, 33%), 292 ([M (^{35}Cl)]$^+$, 100%), 264 ([MH (^{37}Cl)-OMe]$^+$, 4%), 262 ([MH (^{35}Cl)-OMe]$^+$, 14%), 248 ([M (^{37}Cl)-NO_2]$^+$, 10%), 246 ([M (^{35}Cl)-NO_2]$^+$, 3%), 236 ([MH (^{37}Cl)-$COOCH_3$]$^+$, 17%), 234 ([MH (^{35}Cl)-$COOCH_3$]$^+$, 52%); HRMS (ES^+) found ([MH]$^+$) 293.0344; $C_{13}H_{10}{}^{35}ClN_2O_4$ requires M, 293.0329.

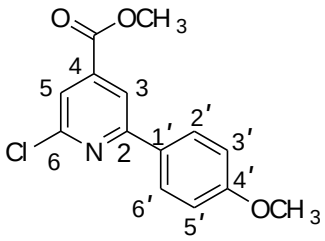
6.2.18.2 *Methyl-6-chloro-2-(3'-thiophen-yl)-pyridine-4-carboxylate* (311)



Methyl-2-chloroisonicotinate **151** (171.5 mg, 1.0 mmol) in MTBE (1.0 ml) was borylated following standard protocol **M1** [[Ir(OMe)cod]$_2$ (33.15 mg, 0.05 mmol, 5 mol%), dtbpy (10 mol%, 26.8 mg) and B_2pin_2 (1.2 mmol, 305 mg) in MTBE (1.5 ml), reaction time= 30 min, reaction temperature= 120 ^oC]. The crude boronate ester (~1.0 mmol) was directly used in Suzuki Miyaura coupling following general procedure **N** with 3-bromothiophene (0.28 ml, 1.5 mmol) at 100 ^oC for 3 h to afford, following chromatography (EtOAc:hexane 1:12), methyl-6-chloro-2-(3'-thiophen-yl)-pyridine-4-carboxylate **311** as a brown solid (25.2 mg, 10 %), (mp = 79.5-80 ^oC); υ_{max} (ATR) 1723 (C=O), 1596, 1550, 1525, 1444, 1432, 1361, 1346, 1290, 1235, 1204, 1198, 1163, 1071, 977, 919, 873, 833, 801, 729, 714, 697, 655 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.04 (1H, d, *J* = 1.0 Hz, 3-*H*) 8.03 (1H, dd, *J* = 3.0, 1.3 Hz, 2'-*H*), 7.7 (1H, d, *J* = 1.0 Hz, 5-*H*), 7.68 (1H, dd, *J* = 5.1, 1.3 Hz, 5'-*H*), 7.4 (1H, dd, *J* = 5.1, 3.0 Hz, 4'-*H*), 4.0 (3H, s, OCH_3); δ_C (176 MHz, $CDCl_3$) 164.7 (*C*=O), 155.0 (*C*-2), 152.1 (*C*-6), 141.0 (*C*-4), 140.1 (*C*-3'), 127.0 (*C*-4'),

126.2 (*C*-5'), 125.7 (*C*-2'), 121.6 (*C*-5), 118.0 (*C*-3), 53.1 (OCH_3); *m/z* (GC-MS, EI^+) 255 ([M (^{37}Cl)]$^+$, 37%), 253 ([M (^{35}Cl)]$^+$, 100%), 224 ([M (^{37}Cl)-OCH_3]$^+$, 8%), 222 ([M (^{35}Cl)-OCH_3]$^+$, 24%), 197 ([MH (^{37}Cl)-$COOCH_3$]$^+$, 8%), 195 ([MH (^{35}Cl)-$COOCH_3$]$^+$, 22%); HRMS (ES^+) found ([MH]$^+$) 254.0052; $C_{11}H_9{}^{35}ClNO_2S$ requires M, 254.0043.

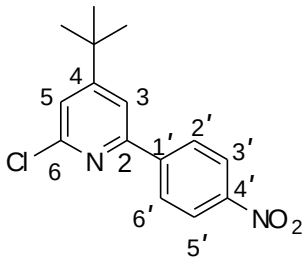
6.2.18.3 *Methyl-6-chloro-2-(4'-methoxyphenyl)-pyridine-4-carboxylate* (312)[88]



Methyl-2-chloroisonicotinate **151** (0.17 g, 1.0 mmol) in MTBE (1.0 ml) was borylated following standard protocol **M1** [[Ir(OMe)cod]$_2$ (33.15 mg, 0.05 mmol, 5 mol%), dtbpy (10 mol%, 26.8 mg) and B_2pin_2 (1.2 mmol, 305 mg) in MTBE (1.5 ml), reaction time= 30 min, reaction temperature= 120 ^oC]. The crude boronate ester (~1.0 mmol) was directly used in Suzuki Miyaura coupling following general procedure **N** with 4-iodoanisole (350 mg, 1.5 mmol) at 100 ^oC for 3 h to afford, following chromatography (EtOAc:hexane 1:10), methyl-6-chloro-2-(4'-methoxyphenyl)-pyridine-4-carboxylate **312** as a white solid (134.5 mg, 48 %), (mp = 101.5-102.5 ^oC); υ_{max} (ATR) 1734 (C=O), 1606, 1597, 1583, 1549, 1519, 1441, 1404, 1390, 1302, 1256, 1180, 1161, 1113, 1071, 1021, 981, 824, 761, 732, 615, 585 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.11 (1H, d, *J* = 1.2 Hz, 3-*H*), 8.03-7.96 (2H, m, 2',6'-*H*), 7.7 (1H, d, *J* = 1.2 Hz, 5-*H*), 7.01-6.93 (2H, m, 3',5'-*H*), 4.0 (3H, s, OC*H*$_3$ ester), 3.86 (3H, s, OC*H*$_3$); δ_C (176 MHz, $CDCl_3$) 164.8 (*C*=O),161.4 (*C*-4'), 158.7 (*C*-2), 152.0 (*C*-6), 140.8 (*C*-4), 129.6 (*C*-1'), 128.6 (*C*-2',6'), 121.1 (*C*-5), 117.3 (*C*-3), 114.4 (*C*-3',5'), 55.5 (4'-O*C*H$_3$), 53.1 (O-*C*H$_3$ ester); *m/z* (GC-MS, EI^+) 279 ([M (^{37}Cl)]$^+$,

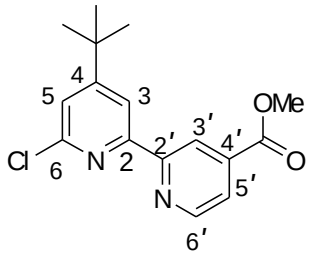
32%), 277 ([M (^{35}Cl)]$^+$, 100%), 264 ([M (^{37}Cl)-CH_3]$^+$, 1%), 262 ([M (^{35}Cl)-CH_3]$^+$, 4%), 248 ([M (^{37}Cl)-OMe]$^+$, 2%), 246 ([M (^{35}Cl)-OMe]$^+$, 4%), 234 & 236 found, 221 ([MH (^{37}Cl)-$C_2H_3O_2$]$^+$, 6%), 219 ([MH (^{35}Cl)-$C_2H_3O_2$]$^+$, 17%); HRMS (ES$^+$) found ([MH]$^+$) 278.0600; $C_{14}H_{13}{}^{35}ClNO_3$ requires M, 278.0584.

6.2.18.4 *4-Tert-butyl-6-chloro-2-(4'-nitrophenyl)-pyridine* (313)



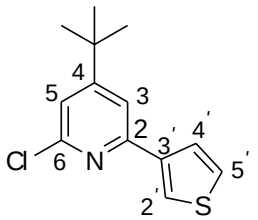
2-Chloro-4-tert-butylpyridine **265** (170 mg, 1.0 mmol) was borylated following standard protocol **M2** [[Ir(OMe)cod]$_2$ (0.01 g, 0.015 mmol, 1.5 mol %), dtbpy (8.0 mg, 0.03 mmol, 3 mol%) and B_2pin_2 (1.0 mmol, 254 mg), reaction time= 1 h, reaction temperature= 80 ^{o}C]. The crude boronate ester (~ 1.0 mmol) was directly used in a Suzuki-Miyaura coupling following general procedure **N,** with 4-iodo-nitrobenzene (374 mg, 1.5 mmol) at 100 ^{o}C for 3 h, to afford, following chromatography (EtOAc:hexane 1:15), 4-tert-butyl-6-chloro-2-(4'-nitrophenyl)-pyridine **313** as an off white solid (117 mg, 40 %), (mp = 192-193 ^{o}C); υ_{max} (ATR), 1588, 1533, 1509, 1410, 1338, 1171, 1104, 856, 813, 762, 731, 698, 644 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.33-8.27 (2H, m, 3',5'-*H*) 8.19-8.12 (2H, m, 2',6'-*H*), 7.69 (1H, d, *J* = 1.5 Hz, 3-*H*), 7.34 (1H, d, *J* = 1.5 Hz, 5-*H*), 1.38 (9H, s, 4-C(C*H*$_3$)$_3$); δ_C (176 MHz, $CDCl_3$) 164.8 (*C*-4), 155.3 (*C*-2), 152.3 (*C*-6), 148.5 (*C*-4'), 144.3 (*C*-1'), 128.0 (*C*-2',6'), 124.1 (*C*-3',5'), 121.4 (*C*-5), 117.2 (*C*-3), 35.5 (4-*C*), 30.6 (4-C-(*C*H$_3$)$_3$)); *m/z* (GC-MS, EI$^+$) 292 ([M(^{37}Cl)]$^+$, 26%), 290 ([M (^{35}Cl)]$^+$, 76%), 277 ([M (^{37}Cl)-CH_3]$^+$, 34%), 275 ([M(^{35}Cl)-CH_3]$^+$, 100%); HRMS (ES$^+$) found ([MH]$^+$) 291.0904; $C_{15}H_{16}{}^{35}ClN_2O_2$ requires M, 291.0900.

6.2.18.5 *4-Tert-butyl-6-chloro-2,2'-bipyridinyl-4'-carboxylic acid methyl ester* (314)



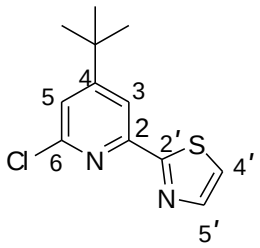
2-Chloro-4-tert-butylpyridine **265** (170 mg, 1.0 mmol) was borylated following standard protocol **M2** [[Ir(OMe)cod]$_2$ (0.01 g, 0.015 mmol, 1.5 mol %), dtbpy (8.0 mg, 0.03 mmol, 3 mol%) and B_2pin_2 (1.0 mmol, 254 mg), reaction time= 1 h, reaction temperature= 80 ^oC]. The crude boronate ester (~ 1.0 mmol) was directly used in Suzuki-Miyaura coupling following general procedure **N,** with methyl-2-bromoisonicotinate (32.4 mg, 1.5 mmol) at 100 ^oC for 3 h, to afford, following chromatography (EtOAc:$CHCl_3$ 1:23), 4-tert-butyl-6-chloro-2,2'-bipyridinyl-4'-carboxylic acid methyl ester **314** as a white solid (200 mg, 66 %), (mp = 102.5-103.5 ^oC); υ_{max} (ATR), 1726 (C=O), 1585, 1532, 1478, 1438, 1373, 1365, 1356, 1315, 1294, 1268, 1165, 1133, 1100, 966, 891, 859, 769, 751, 694, 674, 650 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 8.9 (1H, bs, 3'-*H*) 8.8 (1H, d, *J* = 5.0 Hz, 6'-*H*), 8.4 (1H, d, *J* = 1.6 Hz, 3-*H*), 7.86 (1H, dd, *J* = 5.0, 1.6 Hz, 5'-*H*), 7.3 (1H, d, *J* = 1.6 Hz, 5-*H*), 4.0 (3H, s, OCH_3), 1.38 (9H, s, 4-C(CH_3)$_3$); δ_C (151 MHz, $CDCl_3$) 165.8 (*C*=O), 164.7 (*C*-4), 156.3 (*C*-2'), 155.7 (*C*-2), 151.5 (*C*-6), 150.0 (*C*-6'), 138.7 (*C*-4'), 123.3 (*C*-5'),122.0 (*C*-5), 121.0 (*C*-3'), 117.2 (*C*-3), 52.8 (O-*C*H_3), 35.5 (4-*C*), 30.6 (4-C-(*C*H_3)$_3$)); *m/z* (GC-MS, EI^+) 306 ([M(^{37}Cl)]$^+$, 8%), 304 ([M (^{35}Cl)]$^+$, 25%), 291 ([M (^{37}Cl)-CH_3]$^+$, 37%), 289 ([M (^{35}Cl)-CH_3]$^+$, 100%); HRMS (ES^+) found ([MH]$^+$) 305.1065; $C_{16}H_{17}{}^{35}ClN_2O_2$ requires M, 305.1057.

6.2.18.6 *4-Tert-butyl-6-chloro-2-(3'-thiophen-yl)-pyridine* (315)



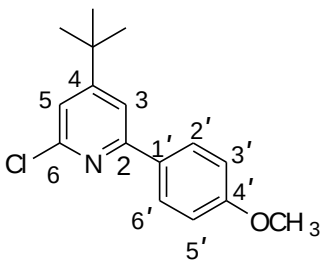
2-Chloro-4-tert-butylpyridine **265** (170 mg, 1.0 mmol) was borylated following standard protocol **M2** [[Ir(OMe)cod]$_2$ (0.01 g, 0.015 mmol, 1.5 mol %), dtbpy (8.0 mg, 0.03 mmol, 3 mol%) and B_2pin_2 (1.0 mmol, 254 mg), reaction time= 1 h, reaction temperature= 80 ^oC]. The crude boronate ester (~ 1.0 mmol) was directly used in Suzuki Miyaura coupling following general procedure **N** with 3-bromothiophene (0.14 ml, 1.5 mmol) at 100 ^oC for 3 h to afford, following chromatography (ether:hexane 1:16), 4-tert-butyl-6-chloro-2-(3'-thiophen-yl)-pyridine **315** as a white solid (168 mg, 67%), (mp = 50-51 ^oC); υ_{max} (ATR) 1591, 1540, 1477, 1434, 1422, 1362, 1346, 1287, 1200, 1165, 1079, 1062, 861, 831, 794, 774, 731, 671 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.95 (1H, dd, *J* = 3.0, 1.3 Hz, 2'-*H*), 7.6 (1H, dd, *J* = 5.0, 1.3 Hz, 4'-*H*), 7.5 (1H, d, *J* = 1.5 Hz, 3-*H*), 7.3 (1H, dd, *J* = 5.0, 3.0 Hz, 5'-*H*), 7.18 (1H, d, *J* = 1.5 Hz, 5-*H*), 1.35 (9H, s, 4-C(C*H*$_3$)$_3$); δ_C (176 MHz, $CDCl_3$) 164.2 (*C*-4), 153.9 (*C*-2), 151.6 (*C*-6), 141.2 (*C*-3'), 126.5 (*C*-5'), 126.3 (*C*-4'), 124.5 (*C*-2'), 119.4 (*C*-5), 116.1 (*C*-3), 35.3 (4-*C*), 30.6 (4-C-(*C*H$_3$)$_3$)); *m/z* (GC-MS, EI$^+$) 253 ([M(^{37}Cl)]$^+$), 37%, 251 ([M (^{35}Cl)]$^+$, 100%), 238 ([M (^{37}Cl)-CH_3)]$^+$, 31%), 236 ([M(^{35}Cl)-CH_3]$^+$, 87%); HRMS (ES$^+$) found ([MH]$^+$) 252.0596; $C_{13}H_{15}{}^{35}ClNS$ requires M, 252.0614.

6.2.18.7 *4-Tert-butyl-6-chloro-2-(2'-thiazol-yl)-pyridine* (316)



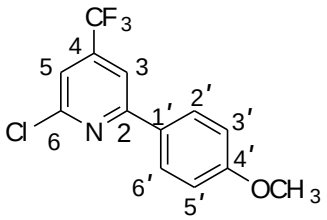
2-Chloro-4-tert-butylpyridine **265** (170 mg, 1.0 mmol) was borylated following standard protocol **M2** [[Ir(OMe)cod]$_2$ (0.01 g, 0.015 mmol, 1.5 mol %), dtbpy (8.0 mg, 0.03 mmol, 3 mol%) and B_2pin_2 (1.0 mmol, 254 mg), reaction time= 1 h, reaction temperature= 80 ^oC]. The crude boronate ester (~ 1.0 mmol) was directly used in Suzuki Miyaura coupling following general procedure **N** with 2-bromothiazole (0.135 ml, 1.5 mmol) at 100 ^oC for 3 h to afford, following chromatography (EtOAc:hexane 1:9), 4-tert-butyl-6-chloro-2-(2'-thiazol-yl)-pyridine **316** as an off white solid (106 mg, 42%), (mp = 96.5-97.5 ^oC); υ_{max} (ATR) 1591, 1541, 1500, 1478, 1440, 1381, 1242, 1168, 1151, 1048, 874, 863, 794, 770, 745, 723, 620, 583, 515 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.12 (1H, d, *J* = 1.5 Hz, 3-*H*) 7.9 (1H, d, *J* = 3.1 Hz, 5'-*H*), 7.5 (1H, d, *J* = 3.1 Hz, 4'-*H*), 7.3 (1H, d, *J* = 1.5 Hz, 5-*H*), 1.36 (9H, s, 4-C(C*H*$_3$)$_3$); δ_C (176 MHz, $CDCl_3$) 168.2 (*C*-2'), 165.0 (*C*-4), 151.6 (*C*-2), 151.4 (*C*-6), 144.1 (*C*-5'), 122.2 (*C*-5), 122.0 (*C*-4'), 115.6 (*C*-3), 35.5 (4-*C*), 30.6 (4-C-(*C*H$_3$)$_3$)); *m/z* (GC-MS, EI$^+$) 254 ([M (^{37}Cl)]$^+$, 24%), 252 ([M (^{35}Cl)]$^+$, 65%), 239 ([M (^{37}Cl)-CH_3]$^+$, 36%), 237 ([M (^{35}Cl)-CH_3]$^+$, 100%); HRMS (ES$^+$) found ([MH]$^+$) 253.0584; $C_{12}H_{15}{}^{35}ClN_2S$ requires M, 253.0566.

6.2.18.8 *4-Tert-butyl-6-chloro-2-(4'-methoxyphenyl)-pyridine* (317)



2-Chloro-4-tert-butylpyridine **265** (170 mg, 1.0 mmol) was borylated following standard protocol **M2** [[Ir(OMe)cod]$_2$ (0.01 g, 0.015 mmol, 1.5 mol %), dtbpy (8.0 mg, 0.03 mmol, 3 mol%) and B_2pin_2 (1.0 mmol, 254 mg), reaction time= 1 h, reaction temperature= 80 ^oC]. The crude boronate ester (~ 1.0 mmol) was directly used in Suzuki Miyaura coupling following general procedure **N** with 4-iodoanisole (350 mg, 1.5 mmol) at 100 ^oC for 3 h to afford, following chromatography (ether:hexane 1:20), 4-tert-butyl-6-chloro-2-(4'-methoxyphenyl)-pyridine **317** as a colorless oil (121 mg, 44 %); υ_{max} (ATR) 1607, 1591, 1535, 1514, 1462, 1410, 1385, 1303, 1247, 1175, 1111, 1074, 1031, 878, 831, 780, 650, 585, 507 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 7.96-7.92 (2H, m, 2', 6'-*H*), 7.55 (1H, d, *J* = 1.5 Hz, 3-*H*), 7.18 (1H, d, *J* = 1.5 Hz, 5-*H*), 7.00-6.95 (2H, m, 3',5'-*H*), 3.86 (3H, s, OC*H*$_3$), 1.35 (9H, s, 4-C(C*H*$_3$)$_3$); δ_C (176 MHz, $CDCl_3$) 164.0 (*C*-4), 160.9 (*C*-4'), 157.7 (*C*-2), 151.6 (*C*-6), 131.0 (*C*-1'), 128.5 (*C*-2', 6'), 119.0 (*C*-5), 115.5 (*C*-3), 114.2 (*C*-3', 5'), 55.5 (O*C*H$_3$), 36.3 (4-*C*), 30.6 (4-C-(*C*H$_3$)$_3$)); *m/z* (GC-MS, EI$^+$) 277 ([M (^{37}Cl)]$^+$, 31%), 275 ([M (^{35}Cl)]$^+$, 100%), 262 ([M (^{37}Cl)-CH$_3$]$^+$, 14%), 260 ([M (^{35}Cl)-CH$_3$]$^+$, 42%); HRMS (ES$^+$) found ([MH]$^+$) 276.1159; $C_{16}H_{19}{}^{35}ClNO$ requires M, 276.1155.

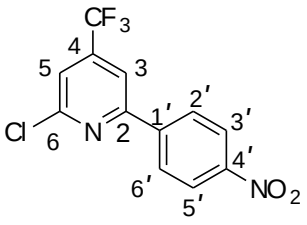
6.2.18.9 *4-Tri-fluoromethyl-6-chloro-2-(4'-methoxyphenyl)-pyridine* (318)



2-Chloro-4-(tri-fluoromethyl)-pyridine **307** (0.13 ml, 1.0 mmol) was borylated following standard protocol **M3** [[Ir(OMe)cod]$_2$ (0.01 g, 0.015 mmol, 1.5 mol %), dtbpy (8.0 mg, 0.03 mmol, 3 mol%) and B_2pin_2 (1.0 mmol, 254 mg), reaction time= 1 h, reaction

temperature= 80 °C]. The crude boronate ester (~ 1.0 mmol) was directly used in Suzuki Miyaura coupling following general procedure **N** with 4-iodoanisole (350 mg, 1.5 mmol) at 100 °C for 3 h to afford, following chromatography (ether:hexane 1:20), 4-tri-fluoromethyl-6-chloro-2-(4'-methoxyphenyl)-pyridine **318** as a yellow oil (105 mg, 36 %);υ_{max} (ATR) 1606, 1557, 1518, 1408, 1394, 1331, 1265, 1253, 1175, 1135, 1098, 1072, 1031, 830, 694, 665, 581 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 7.99-7.94 (2H, m, 2',6'-*H*), 7.73 (1H, *d, J* = 0.6 Hz, 3-*H*), 7.37 (1H, *d, J* = 0.6 Hz, 5-*H*), 6.99-6.94 (2H, m, 3',5'-*H*), 3.85 (3H, s, OC*H*$_3$); δ_C (176 MHz, $CDCl_3$) 161.7 (*C*-4'), 159.1 (*C*-2), 151.2 (*C*-6), 141.5 (q, *J* = 34.1 Hz*, C*-4), 129.0 (*C*-1'), 128.6 (*C*-2',6'), 122.4 (q, *J* = 273 Hz*, C*F_3), 117.0 (q, *J* = 3.7 Hz, *C*-5), 114.4 (*C*-3',5'), 113.4 (q, *J* = 3.7 Hz, *C*-3), 55.4 (O-*C*H_3); *m/z* (GC-MS, EI^+) 289 ([M (^{37}Cl)]$^+$, 33%), 287 ([M (^{35}Cl)]$^+$, 100%), 274 ([M (^{37}Cl)-CH_3]$^+$, 3%), 272 ([M (^{35}Cl)-CH_3]$^+$, 9%), 246 & 244 found; HRMS (ES^+) found ([MH]$^+$) 288.0401; $C_{13}H_{10}{}^{35}ClF_3NO$ requires M, 288.0403.

6.2.18.10 *4-Tri-fluoromethyl-6-chloro-2(4'-nitrophenyl)-pyridine* (319)



2-Chloro-4-(tri-fluoromethyl)-pyridine **307** (0.13 ml, 1.0 mmol) was borylated following standard protocol **M3** [[Ir(OMe)cod]$_2$ (0.01 g, 0.015 mmol, 1.5 mol %), dtbpy (8.0 mg, 0.03 mmol, 3 mol%) and B_2pin_2 (1.0 mmol, 254 mg), reaction time= 1 h, reaction temperature= 80 °C]. The crude boronate ester (~ 1.0 mmol) was directly used in Suzuki Miyaura coupling following general procedure **N** with 4-iodonitrobenzene (350

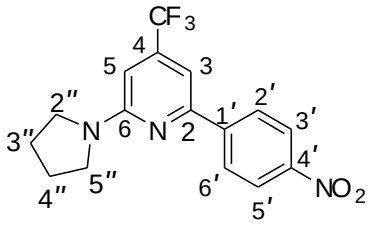
mg, 1.5 mmol) at 100 °C for 3 h to afford, following chromatography (toluene:hexane 1:1), 4-tri-fluoromethyl-6-chloro-2(4'-nitrophenyl)-pyridine **319** as an off white solid (175 mg, 58 %), (mp = 120-121 °C); υ_{max} (ATR) 1601, 1564, 1516, 1409, 1350, 1328, 1263, 1173, 1140, 1101, 1071, 860, 873, 818, 760, 707, 696, 675 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.36-8.33 (2H, m, 3',5'-*H*), 8.24-8.20 (2H, m, 2',6'-*H*), 7.9 (1H, *s*, 3-*H*), 7.6 (1Hs,5-*H*); δ_C (176 MHz, $CDCl_3$) 156.9 (*C*-2), 153.0 (*C*-6), 149.2 (C-4'), 142.3 (*q, J* = 34.7 Hz*, C*-4), 142.1 (*C*-1'), 128.2 (*C*-2',6'), 124.3 (*C*-3',5'), 122.1 (q, *J* = 274 Hz, *C*F_3), 120.3 (q, *J* = 3.6 Hz, *C*-5), 115.4 (q, *J* = 3.4 Hz, *C*-3); *m/z* (GC-MS, EI^+) 304 ([M] (^{37}Cl)]$^+$, 31%), 302 ([M] (^{35}Cl)]$^+$, 100%), 285 ([M] (^{37}Cl)-F]$^+$, 3%), 283 ([M] (^{35}Cl)-F]$^+$, 10%), 274 ([M] (^{37}Cl)-NO]$^+$, 8%), 272 ([M] (^{35}Cl)-NO]$^+$, 23%), 258 ([M] (^{37}Cl)-NO_2]$^+$, 14%), 256 ([M] (^{35}Cl)-NO_2]$^+$, 43%), 246 & 244 found; HRMS (ES^+) found ([MH]$^+$) 303.0138; $C_{12}H_7{}^{35}ClF_3N_2O_2$ requires M, 303.0148.

6.2.19 General procedure O: Preparation of multidirectionalpyridine derivatives[111]

2- or 6-Chloropyridine derivatives (1 mmol) was placed in the vessel which was then sealed, evacuated, backfilled with N_2 and secondary amine (excess amount) was then added. The reaction mixture was heated in μW reactor at the 130 °C for the stated period. After cooling the reaction mixture, DCM (2 x 10 ml) was then added to the reaction mixture, and then washed with $NaHCO_3$ (aq.). The organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo* to afford following chromatography the desired product.

6.2.19.1 *4-Tri-fluoromethyl-6-(N-pyrrolidin-yl)-2(4'-nitrophenyl)-pyridine*

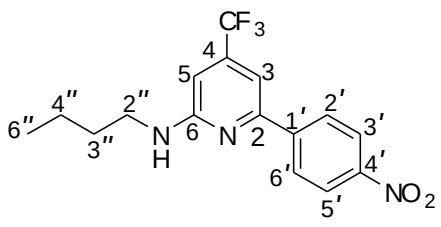
(320)



Following procedure **O**, 4-tri-fluoromethyl-6-chloro-2(4'-nitrophenyl)-pyridine **319** (303 mg, 1.0 mmol) and pyrrolidine (0.46 ml, 5.5 mmol) were combiend at 130 °C for 1 h to afford, following (EtOAc:hexane 1:12), 4-tri-fluoromethyl-6-(N-pyrrolidin-yl)-2(4'-nitrophenyl)-pyridine **320** as an off yellow soli (263 mg, 78 %), (mp = 211.5-212.5 °C); υ_{max} (ATR) 1616, 1601, 1564, 1519, 1492, 1480, 1443, 1390, 1344, 1322, 1290, 1249, 1159, 1108, 1093, 1010, 972, 849, 826, 756, 722, 694, 671 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.31-8.27 (2H, m, 3',5'-*H*), 8.22-8.18 (2H, m, 2',6'-*H*), 7.19 (1H, s, 3-*H*), 6.57 (1H, s, 5-*H*), 3.63-3.59 (4H, m, 2",5"-*H*), 2.11-2.04 (4H, m, 3", 4"-*H*); δ_C (176 MHz, $CDCl_3$) 157.16 (*C*-6), 154.3 (*C*-2), 148.3 (*C*-4'), 145.1 (*C*-1'), 140.39 (q, *J* = 32.9, *C*-4), 127.7 (*C*-2',6'), 123.9 (*C*-3',5'), 123.43 (q, *J* = 273 Hz, *C*F_3), 103.6 (q, *J* = 3.3 Hz, *C*-3), 102.44 (q, *J* = 4.0 Hz, *C*-5), 47.1 (*C*-2",5"), 25.6 (*C*-3",4"); *m/z* (GC-MS, EI^+) 337 ($[M]^+$, 39%), 309 ($[MH-C_2H_5]^+$, 28%), 308 ($[M-C_2H_5]^+$, 100%), 262 ($[M-C_2H_5NO_2]^+$, 26%); HRMS (ES^+) found ($[MH]^+$) 338.1105; $C_{16}H_{15}F_3N_3O_2$ requires M, 338.1116.

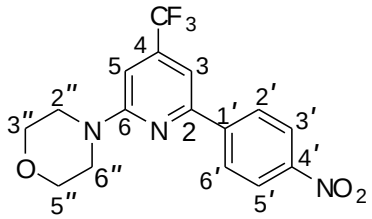
6.2.19.2 *Butyl-[6-(4'-nitrophenyl)-4-tri-fluoromethylpyridine-2-yl]-amine*

(321)



Following procedure **O**, 4-tri-fluoromethyl-6-chloro-2(4'-nitrophenyl)-pyridine **319** (303 mg, 1.0 mmol) and butylamine (0.54 ml, 5.5 mmol) were combiend at 130 ^{o}C for 1 h to afford, following chromatography (EtOAc:hexane 1:12), Butyl-[6-(4'-nitrophenyl)-4-tri-fluoromethylpyridine-2-yl]-amine **321** as a yellow solid (255 mg, 75 %), (mp = 162.8-163.8 ^{o}C); υ_{max} (ATR) 3401 (*N*H), 1625, 1604, 1573, 1533, 1459, 1413, 1396, 1331, 1257, 1158, 1117, 1096, 860, 830, 757, 723, 695, 678, 639 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.31-8.26 (2H, m, 3',5'-*H*), 8.18-8.11 (2H, m, 2',6'-*H*), 7.2 (1H, d, *J* = 0.6 Hz, 3-*H*), 6.6 (1H, s, 5-*H*), 4.9 (1H, s broad, *NH*), 3.44-3.39 (2H, m, 2"-*H*), 1.69-1.64 (2H, m, 3"-*H*), 1.5-1.44 (2H, m, 4"-*H*), 1.0 (3H, t, *J* = 7.4 Hz, 5"-*H*); δ_C (176 MHz, $CDCl_3$) 159.1 (*C*-6), 154.7 (*C*-2'), 148.4 (*C*-4'), 144.7 (*C*-1'), 140.8 (q, *J* = 33.2 Hz, *C*-4), 127.7 (*C*-2',6'), 124.0 *(C*-3',5'), 123.2 (q, *J* = 273 Hz, *C*F_3), 105.3 (q, *J* = 3.3 Hz, *C*-3), 102.8 (*C*-5), 42.0 (*C*-2"), 31.6 (*C*-3"), 20.3 (*C*-4"), 14.0 (*C*-5"); *m/z* (GC-MS, EI$^+$) 339 ([M]$^+$, 31%), 320 ([M-F]$^+$, 8%), 310 ([M-C_2H_5]$^+$, 52%), 296 ([M-C_3H_7]$^+$, 100%), 283 ([MH-C_2H_5]$^+$, ([MH-F_3]$^+$ 61%), ([M-$C_3H_7NO_2$]$^+$, 60%); HRMS (ES$^+$) found ([MH]$^+$) 340.1276; $C_{16}H_{17}F_3N_3O_2$ requires M, 340.1273.

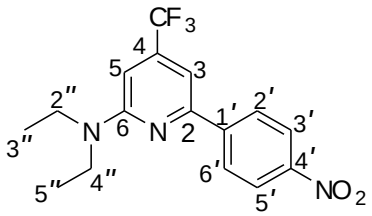
6.2.19.3 *4-Tri-fluoromethyl-6-(N-morpholin-yl)-2(4'-nitrophenyl)-pyridine* (322)



Following procedure **O**, 4-tri-fluoromethyl-6-chloro-2(4'-nitrophenyl)-pyridine **319** (303 mg, 1.0 mmol) and morpholine (0.48 ml, 5.5 mmol) were combined at 130 ^{o}C for 1 h to afford, following chromatography (EtOAc:hexane 1:8), 4-tri-fluoromethyl-6-(N-

morpholin-yl)-2(4'-nitrophenyl)-pyridine **322** as a yellow solid (325 mg, 92 %), (mp = 267.5-268.5 ^{o}C); υ_{max} (ATR) 1603, 1567, 1517, 1438, 1324, 1302, 1242, 1161, 1111, 982, 967, 847, 825, 757, 711, 695, 675 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.35-8.26 (2H, m, 3',5'-*H*), 8.23-8.12 (2H, m, 2',6'-*H*), 7.33 (1H, s, 3-*H*), 6.85 (1H, s, 5-*H*), 3.9-3.86 (4H, m, 3",5"-*H*), 3.71-3.67 (4H, m, 2",6"-*H*); δ_C (176 MHz, $CDCl_3$) 159.4 (*C*-6), 154.4 (*C*-2), 148.5 (C-4'), 144.6 (C-1'), 141.3 (q, *J* = 33.0 Hz, *C*-4), 127 (*C*-2', 6'), 124.1 *(C*-3', 5'), 123.2 (q, *J* = 273 Hz, *C*F_3), 106.1 (q, *J* = 3.3 Hz, *C*-3), 102.6 (q, *J* = 4.0 Hz, *C*-5), 66.7 (*C*-3",5"), 45.4 (*C*-2",6"); *m/z* (GC-MS, EI$^+$) 353 ([M]$^+$, 68%), 334 ([M-F]$^+$, 17%), 322 ([MH-O_2]$^+$, 100%), 308 ([MH-NO_2]$^+$, 24%), 296 ([M-F_3]$^+$, 73%), 353 ([M-CF_3O]$^+$, 76%); HRMS (ASAP) found ([MH]$^+$) 354.1067; $C_{16}H_{15}F_3N_3O_3$ requires M, 354.1066.

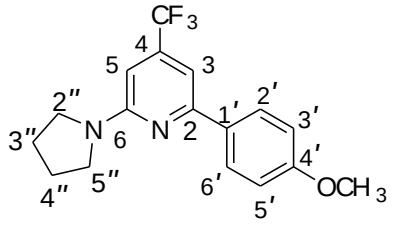
6.2.19.4 ***Di-ethyl-[6-(4'-nitrophenyl)-4-tri-fluoromethylpyridine-2-yl]-amine*** **(323)**



Following procedure **O**, 4-tri-fluoromethyl-6-chloro-2(4'-nitrophenyl)-pyridine **319** (303 mg, 1.0 mmol) and di-ethylamine (3.0 ml, 29.0 mmol) were combiend at 130 ^{o}C for 6 h to afford, following chromatography (EtOAc:hexane 1:12), di-ethyl-[6-(4'-nitrophenyl)-4-tri-fluoromethylpyridine-2-yl]-amine **323** as a yellow solid (207 mg, 61 %), (mp = 87.9-88.9 ^{o}C); υ_{max} (ATR) 1616, 1601, 1566, 1516, 1503, 1442, 1349, 1344, 1332, 1263, 1249, 1175, 1123, 1110, 979, 853, 829, 758, 710, 695, 676 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.32-8.27 (2H, m, 3',5'-*H*), 8.21-8.15 (2H, m, 2',6'-*H*), 7.20 (1H, s, 3-*H*), 6.7 (1H, s, 5-*H*),

3.63-3.59 (4H, q, *J* = 7.1 Hz, 2",4"-*H*), 1.26 (6H, t, *J* = 7.1 Hz, 3",5"-*H*); δ_C (176 MHz, $CDCl_3$) 157.5 (*C*-6), 154.3 (*C*-2), 148.3 (*C*-4'), 145.2 (*C*-1'), 140.7 (q, *J* = 32.7, *C*-4), 127.6 (*C*-2',6'), 124.0 (*C*-3',5'), 123.4 (q, *J* = 273 Hz, *C*F_3), 103.5 (q, *J* = 3.3 Hz, *C*-3), 101.4 (q, *J* = 4.0 Hz, *C*-5), 43.13 (*C*-2",4"), 12.9 (*C*-3",5"); *m/z* (GC-MS, EI^+) 339 ($[M]^+$, 43%), 324 ($[M-CH_3]^+$, 64%), 310 ($[M-C_2H_5]^+$, 100%), 296 ($[MH-C_3H_8]^+$, 56%), 264 ($[M-C_2H_5NO_2]^+$, 31%); HRMS (ES^+) found ($[MH]^+$) 340.1270; $C_{16}H_{17}F_3N_3O_2$ requires M, 340.1273.

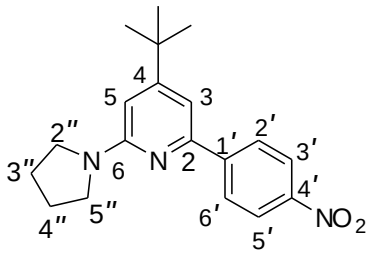
6.2.19.5 ***4-Tri-fluoromethyl-6-(N-pyrrolidin-yl)-2-(4'-methoxyphenyl)-pyridine*** **(324)**



Following procedure **O**, the crude mixture of 4-tri-fluoromethyl-6-chloro-2-(4'-methoxyphenyl)-pyridine in **6.2.18.9** (~1.0 mmol) and pyrrolidine (0.46 ml, 5.5 mmol) were combined at 130 ^oC for 30 min to afford, following chromatography (ether:hexane 1:20), 4-tri-fluoromethyl-6-(*N*-pyrrolidin-yl)-2(4'-methoxyphenyl)-pyridine **324** as an off white solid (65 mg, 20 %), (mp = 103.3-104.5 ^oC); υ_{max} (ATR) 1613, 1563, 1497, 1460 1439, 1408, 1389, 1351, 1333, 1304, 1293,1246, 1183, 1157, 1120, 1105, 1097, 1051, 1032, 1014, 1004, 842, 825, 804, 782, 711, 680, 671, 648, 637, 618, 586, 522, 504 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.06-8.00 (2H, m, 2', 6'-*H*), 7.11 (1H, s, 3-*H*), 7.01-6.96 (2H, m, 3',5'-*H*), 6.42 (1H, s, 5-*H*), 3.86 (3H, s, OCH_3), 3.64-3.53 (4H, m, 2",5"-*H*), 2.08-2.00 (4H, m, 3",4"-*H*); δ_C (176 MHz, $CDCl_3$) 160.7 (*C*-4'),157.0 (*C*-6), 156.6 (*C*-2), 140.0 (q, *J* = 32.4 Hz, *C*-4), 132.0 (*C*-1'), 128.3 (*C*-2',6'), 123.77 (q, *J* = 273 Hz, *C*F_3),

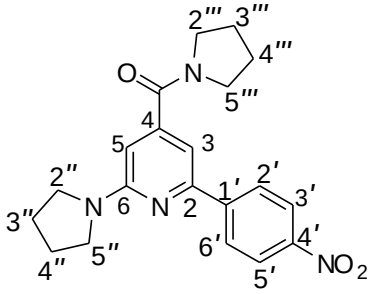
114.0 (*C*-3',5'), 102.1 (q, *J* = 3.4 Hz, *C*-3), 100.0 (q, *J* = 4.0 Hz, *C*-5), 55.4 (O-*C*H_3), 46.9 (*C*-2",5"), 25.6 (*C*-3",4"); *m/z* (GC-MS, EI^+) 323 ($[MH]^+$, 7%), 322 ($[M]^+$, 42%), 293 ($[MH-OCH_3]^+$, 100%); HRMS (ES^+) found ($[MH]^+$) 323.1364; $C_{17}H_{18}F_3N_2O$ requires M, 323.1371.

6.2.19.6 *4-Tert-butyl-6-(N-pyrrolidin-yl)-2(4-methoxyphenyl)-pyridine* (325)



Following procedure **O**, 4-tert-butyl-6-chloro-2-(4'-nitrophenyl)-pyridine **313** (291 mg, 1.0 mmol) and pyrrolidine (0.46 ml, 5.5 mmol) were combiend at 130 ^oC for 30 min to afford, following chromatography (EtOAc:hexane 1:15), 4-tert-butyl-6-(*N*-pyrrolidin-yl)-2(4'-methoxyphenyl)-pyridine **325** as a red solid (100 mg, 31 %), (mp = 180.5-182.5 ^oC); υ_{max} (ATR) 1597, 1549, 1501, 1476, 1456, 1323, 1107, 1101, 1011, 865, 850, 842, 832, 760, 698, 659, 631, 495 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.3-8.23 (2H, m, 3',5'-*H*), 8.21-8.17 (2H, m, 2',6'-*H*), 7.09 (1H, d, *J* = 1.3 Hz, 3-*H*), 6.38 (1H, d, *J* = 1.3 Hz, 5-*H*), 3.55-3.60 (4H, m, 2",5"-*H*), 2.06-2.01 (4H, m, 3",4"-*H*), 1.35 (9H, s, C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 161.9 (*C*-4),157.7 (*C*-6), 152.6 (*C*-2), 147.7 (*C*-4'), 146.9 (*C*-4'), 127.6 (*C*-2',6'), 123.8 (*C*-3',5'), 107.03 (*C*-3), 103.4 (*C*-5), 47.0 (*C*-2",5"), 35.12 (*4-C*), 30.8 (4-C-(*C*H_3)$_3$)), 25.7 (*C*-3", 4"); *m/z* (GC-MS, EI^+) 326 ($[MH]^+$, 16%), 325 ($[M]^+$, 78%), 296 ($[MH-(CH_3)_2]^+$, 16%); HRMS (ES^+) found ($[MH]^+$) 326.1869; $C_{19}H_{24}N_3O_2$ requires M, 326.1869.

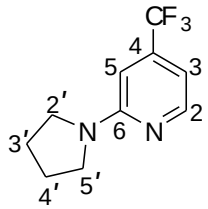
6.2.19.7 *[2-(4'-Nitrophenyl)-6-pyrrolidin-1-yl-pyridin-4-yl]-pyrrolidin-1-yl-methanone* (327)



Following procedure **O**, 4-tri-fluoromethyl-6-chloro-2(4'-nitrophenyl)-pyridine **310** (293 mg, 1.0 mmol) and pyrrolidine (0.92 ml, 11.0 mmol) were combiend at 130 ^{o}C for 1 h to afford, following chromatography (EtOAc:hexane 1:1), [2-(4'-nitrophenyl)-6-pyrrolidin-1-yl-pyridin-4-yl]-pyrrolidin-1-yl-methanone **327** as a yellow solid (275 mg, 75 %), (mp = 239.5-240.5 ^{o}C); υ_{max} (ATR) 1618, 1616, 1598, 1541, 1512, 1478, 1456, 1442, 1419, 1344, 1322, 1102, 858, 755, 702, 513 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.29-8.21 (2H, m, 3',5'-*H*), 8.21-8.14 (2H, m, 2',6'-*H*), 7.1 (1H, s, 3-*H*), 6.4 (1H, s, 5-*H*), 3.7 (2H, t, *J* = 7.0 Hz, 2"'-*H*), 3.60-3.49 (4H, m, 2",5"-*H*), 3.43 (2H, t, *J* = 6.7 Hz, 5"'-*H*), 2.06-2.01 (4H, m, 3",4"-*H*), 2.0 (2H, p, *J* = 7.0 Hz, 3"'-*H*), 1.9 (2H, p, *J* = 6.7 Hz, 4"'-*H*); δ_C (125 MHz, $CDCl_3$) 168.4 (*C*=O), 157.2 (*C*-6), 153.3 (*C*-2), 148.0 (*C*-4'), 146.9 (*C*-4), 145.8 (*C*-1'), 127.5 (*C*-2',6'), 123.8 (*C*-3',5'), 106.0 (*C*-3), 104.1 (*C*-5), 49.4 (*C*-5"'), 46.9 (C-2",5"), 46.2 (*C*-2"'), 26.4 (*C*-4"'), 25.6 (*C*-3",4"), 24.5 (*C*-3"'); *m/z* (LC-MS, ES$^+$) 1121 ([M_3Na]$^+$, 38%), 755 ([M_2Na]$^+$, 81%), 366 ([M]$^+$, 100%); HRMS (ES$^+$) found ([MH]$^+$) 367.1781; $C_{20}H_{23}N_4O_3$ requires M, 367.1770.

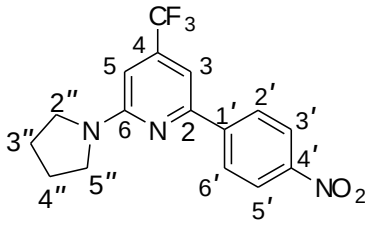
6.2.19.8 *4-Tri-fluoromethyl-6-(N-pyrrolidin-yl)-2(4'-nitrophenyl)-pyridine* (320)

6.2.19.8.1 *4-Tri-fluoromethyl-6-(N-pyrrolidin-yl)-pyridine* (328)[145]



Following procedure **O**, 2-chloro-4-tri-fluoromethylpyridine **307** (128 µl) and pyrrolidine (0.46 ml, 5.5 mmol) were combined at 130 °C for 1h to afford, following chromatography (EtOAc:hexane 1:10), 4-tri-fluoromethyl-6-(*N*-pyrrolidin-yl)-pyridine **328** as a white solid (195 mg, 90 %), (mp = 57.2-58 °C); υ_{max} (ATR) 1611, 1559, 1505, 1460, 1335, 1310, 1288, 1165, 1118, 1101, 1006, 841, 813, 679, 666, 488, 460 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.32 (1H, d, *J* = 5.2 Hz, 2-*H*), 6.6 (1H, dd, *J* = 1.5, 5.2 Hz, 3-*H*), 6.47 (1H, s, 5-*H*), 3.49-3.37 (2H, m, 2',5'-*H*), 2.03-1.93 (2H, m, 3',4'-*H*); δ_C (176 MHz, $CDCl_3$) 157.4 (*C*-6), 149.5 (*C*-2), 139.2 (q, *J* = 32.9 Hz, *C*-4), 123.4 (q, *J* = 273 Hz, *C*F_3), 106 (q, *J* = 3.3 Hz, *C*-3), 102.1 (q, *J* = 4.2 Hz, *C*-5), 46.9 (*C*-2',5'), 25.5 (*C*-3',4'); *m/z* (GC-MS, EI^+) 216 ($[M]^+$, 41%), 187 ($[M\text{-}C_2H_5]^+$, 100%), 188 ($[M\text{-}C_2H_4]^+$, 35%), 161 ($[MH\text{-}C_4H_8]^+$, 18%), 146 ($[M\text{-}C_4H_8N]^+$, 21%), 147 ($[MH\text{-}C_4H_8N]^+$, 18%); HRMS (ES^+) found ($[MH]^+$) 217.0962; $C_{10}H_{12}F_3N_2$ requires M, 217.0953.

6.2.19.8.2 *4-Tri-fluoromethyl-6-(N-pyrrolidin-yl)-2(4'-nitrophenyl)-pyridine* (320)



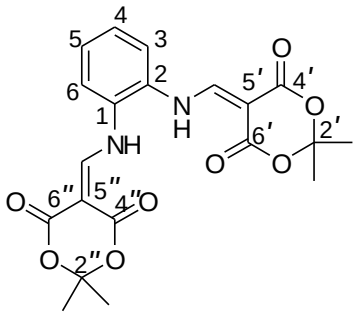
4-Tri-fluoromethyl-6-(*N*-pyrrolidin-yl)-pyridine **328** (216 mg, 1.0 mmol) in MTBE (1.0 ml) was borylated following standard protocol **M2** [[Ir(OMe)cod]$_2$ (33.15 mg, 0.05 mmol, 5 mol%), dtbpy (8.0 mg 0.03 mmol, 3 mol%) and B_2pin_2 (1.2 mmol, 305 mg) in MTBE (1.0 ml), reaction time= 3 h, reaction temperature= 80 ^oC]. The crude boronate ester (~ 1.0 mmol) was directly used in Suzuki Miyaura coupling following general procedure **N** with 4-iodonitrobenzene (350 mg, 1.5 mmol) at 100 ^oC for 3 h to afford, following chromatography (EtOAc:hexane 1:12), 4-tri-fluoromethyl-6-(*N*-pyrrolidin-yl)-2(4-nitrophenyl)-pyridine **320** as an off yellow soli (165 mg, 49 %); Data have been identified above in (**Section 6.2.19.1**).

Chapter 5

6.2.20 Preparation of 1,2-bis-[(2,2-di-methyl-4,6-dioxo-1,3-dioxan-5-ylidenemethyl)-amino]benzene derivatives, procedure P:

In a round bottom flask equipped with a condenser, a mixture of Meldrum's acid (6.72 g, 46.6 mmol) and tri-methyl *ortho*formate (50 ml, 457 mmol) were heated under reflux at 101 ^{o}C for 2 h. The reaction temperature was then cooled to 80 ^{o}C, and the 1,2-phenylenediamine derivative (20 mmol) added portionwise. The reaction mixture was then refluxed at 101 ^{o}C for an additional 1 h, resulting a solid product. The reaction mixture was cooled to r.t and then filtered *in vacuo* to afford, following washing with ether, the desired product was isolated requiring no further purification.

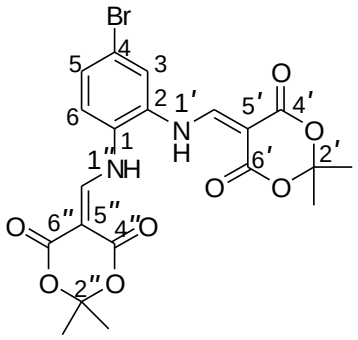
6.2.20.1 *1,2-Bis-[(2,2-di-methyl-4,6-dioxo-1,3-dioxan-5-ylidenemethyl)-amino]-benzene* (337)[112]



Following procedure **P**, Meldrum's acid, tri-methyl *ortho*formate and *1,2*-phenylenediamine **334** (2.16 g) were combined to afford 1,2-bis-[(2,2-di-methyl-4,6-dioxo-1,3-dioxan-5-ylidenemethyl)-amino]-benzene **337** as an off white solid (6.8 g, 82%), (mp > 200 ^{o}C, decomp., lit.,[112] 208-210 ^{o}C, decomp.); υ_{max} (ATR) 3264 (NH), 1725 (C=O), 1674, 1612, 1568, 1426, 1365, 1305, 1262, 1216, 1199, 1138, 999, 931, 804, 786, 756, 704, 646, 604, 544, 500, cm^{-1}; δ_H (700 MHz, $CDCl_3$) 11.3 (2H, d, *J* = 13.5 Hz,

NH), 8.5 (2H, d, *J* = 13.5 Hz, *CH*-*N*H), 7.4 (4H, m, Ar-*H*), 1.8 (12H, s, 2',2"-(C*H*$_3$)$_4$); δ_C (176 MHz, $CDCl_3$) 166.0 (*C*=*O*), 163.2 (*C*=O), 155.0 (*C*H-*N*H), 131.1 (*C*-1 and *C*-2), 129.0 (*C*-3 and *C*-6), 121.3 (*C*-5 and *C*-4), 106.0 (*C*-2' and *C*-2"), 90.0 (*C*-5' and *C*-5"), 27.3 (2',2"-C(*C*H$_3$)$_4$) ; *m/z* (LC-MS, ES$^+$) 854 ([M_2-H+Na]$^+$, 100%), 855 ([M_2 +Na]$^+$, 28%).

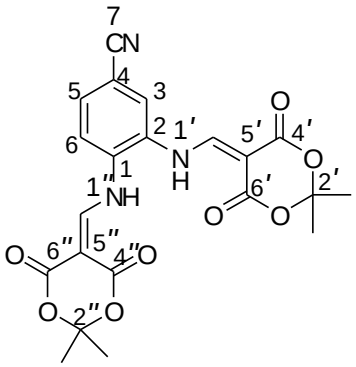
6.2.20.2 ***4-Bromo-1,2-bis-[(2,2-di-methyl-4,6-dioxo-1,3-dioxane-5-ylidenemethyl)-amino]-benzene*** **(340)**



Following procedure **P**, Meldrum's acid, tri-methyl *ortho*formate and 4-bromo1,2-phenylenediamine **338** (3.75 g) were combined to afford 4-bromo-1,2-bis-[(2,2-di-methyl-4,6-dioxo-1,3-dioxane-5-ylidenemethyl)-amino]-benzene **340** as a brown solid (5.9 g, 60%), (mp > 200 ^oC, decomp.); υ_{max} (ATR) 3165 (*N*H), 1724(C=O), 1665, 1629, 1606, 1564, 1429, 1415, 1388, 1263, 1198, 1143, 1026, 966, 927, 888, 803, 755, 731, 662, 647, 575, 502, 468, 441 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 11.32 (1H, d, *J* = 13.4 Hz, 1'-*NH*), 11.27 (1H, d, *J* = 13.5 Hz, 1"-*NH*), 8.5 (1H, d, *J* = 13.4 Hz, 5'-C*H*), 8.4 (1H, d, *J* = 13.5 Hz, 5"-C*H*), 7.6 (1H, d, *J* = 2.1 Hz, 3-*H*), 7.5 (1H, dd, *J* = 2.1 Hz, *J* = 8.6 Hz, 5-*H*), 7.3 (1H, d, *J* = 8.6 Hz, 6-*H*), 1.7 (12H, s, 2',2"-(C*H*$_3$)$_4$); δ_C (176 MHz, $CDCl_3$) 165.5 (*C*=O), 165.4 (*C*=O), 163.0 (*C*=O), 162.9 (*C*=O), 154.9 (5"-*CH*), 154.5 (5'-*CH*), 132.4 (*C*-2), 131.4 (*C*-5), 130.2 (*C*-1), 124.2 (*C*-3), 122.8 (*C*-6), 121.6 (*C*-4), 105.8 (2',2"-(*C*H$_3$)$_2$), 105.7 (2',2"-(*C*H$_3$)$_2$), 90.3 (*C*-5'), 90.0 (*C*-5"), 27.3 (2',2"-(*C*H$_3$)$_4$); *m/z* (LC-MS, ES$^+$) 1012 ([M_2H+Na (^{79}Br)]$^+$,

100%), 1014 ([M_2H+Na (^{81}Br)]$^+$, 80%); HRMS (ES$^+$) found ([M_2+Na]$^+$) 1011.0571; $C_{40}H_{38}{}^{79}Br_2N_4NaO_{16}$ requires M, 1011.0547.

6.2.20.3 *4-Cyano-1,2-bis-[(2,2-di-methyl-4,6-dioxo-1,3-dioxane-5-ylidenemethyl)-amino]-benzene* (341)

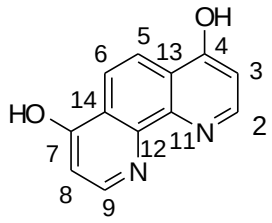


Following procedure **P**, Meldrum's acid, tri-methyl *ortho*formate and 3,4-di-aminobenzonitrile **339** (2.66 g) were heated at 101 ^{o}C to afford 4-Cyano-1,2-bis-[(2,2-di-methyl-4,6-dioxo-1,3-dioxane-5-ylidenemethyl)-amino]-benzene **341** as a brown solid (5.9 g, 60%), (mp > 200 ^{o}C, decomp.); υ_{max} (ATR) 3120 (*N*H), 2239(C*N*), 1724(C=O), 1716, 1674, 1629, 1571, 1436, 1425, 1392,1380, 1266, 1220, 1193, 1140, 999, 917, 855, 805, 788, 643, 619, 508, 414 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 11.6 (1H, d, *J* = 13.1 Hz, 1"-*NH*), 11.3 (1H, d, *J* = 13.2 Hz, 1'-*NH*), 8.58 (1H, d, *J* = 13.1 Hz, 5"-C*H*), 8.44 (1H, d, *J* = 13.2 Hz, 5'-C*H*), 7.82-7.63 (2H, m, 3,5-*H*), 7.55 (1H, d, *J* = 8.9 Hz, 6-*H*), 1.77-1.76 (12H, s, 2',2"-(C*H*$_3$)$_4$); δ_C (176 MHz, $CDCl_3$) 165.5 (*C*=O), 165.4 (*C*=O), 162.6 (*C*=O), 162.5 (*C*=O), 155.15 (5'-*CH*), 152.8 (5"-*CH*), 135.2 (*C*-1), 132.3 (Ar-*C*), 131.1 (*C*-2), 126.1 (Ar-*C*), 120.0 (*C*-6), 116.8 (4-*CN*), 111.5 (*C*-4), 106.0 (2',2"-(*C*H$_3$)$_4$), 91.7 (*C*-5"), 91.2 (*C*-5'), 27.43 (2',2"-*C*H$_3$), 27.39 (2',2"-*C*H$_3$); *m/z* (LC-MS, ES$^+$) 904 ([M_2-H+Na]$^+$, 100%); HRMS (ES$^+$) found ([M_2+Na]$^+$) 905.2257; $C_{42}H_{38}N_6NaO_{16}$ requires M, 905.2242.

6.2.21 Preparation of [1,10]-phenanthroline derivatives, procedure Q:[112]

In a round two neck bottom flask equipped with a long condenser, under N_2, 1,2-bis-[(2,2-di-methyl-4,6-dioxo-1,3-dioxan-5-ylidenemethyl)-amino]-benzene derivatives (2.0 mmol) were added in small portions to di-phenyl ether (21 ml) at 240 ^oC resulting in vigorous gas evolution. The reaction temperature was then increased to 260 ^oC for 30 min. The reaction mixture was then allowed to cool to 80 ^oC and isolated by filtration to afford, following washing with acetone, hexane and ether, the title phenanthroline compound without requiring further purification.

6.2.21.1 *4,7-Di-hydroxy-[1,10]-phenanthroline* (342)[112]



Following procedure **Q**, 1,2-bis-[(2,2-di-methyl-4,6-dioxo-1,3-dioxan-5-ylidenemethyl)-amino]-benzene **337** (0.832 g) was heated in di-phenylether to afford, following washing with acetone, hexane and ether, 4,7-di-hydroxy-[1,10]-phenanthroline **342** as a brown solid (255 mg, 60%), (mp > 300 ^oC, decomp., lit.,[112] stable up to 250 ^oC); υ_{max} (ATR) 3333(OH), 1505, 1386, 1307, 1236, 1190, 907, 821, 698, 685, 661, 544, 506 cm^{-1}; δ_H (400 MHz, NaOD) 8.1 (2H, d, *J* = 5.6 Hz, 2,9-*H*), 7.6(2H, s, 5,6-*H*), 6.3 (2H, d, *J* = 5.6 Hz, 3,8-*H*); *m/z* (LC-MS, ES^+) 212 ($[M]^+$, 100%), 213 ($[MH]^+$, 72%), 424 ($[M_2]^+$, 57%).

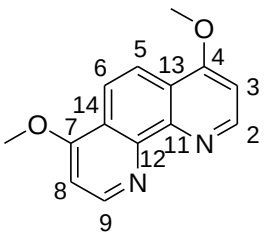
6.2.22 Preparation of mono- and di-alkylation of 4,7-di-hydroxy-[1,10]-phenanthroline derivatives

6.2.22.1 Procedure R[113]

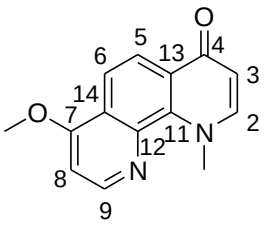
In a round bottomed flask, 4,7-di-hydroxy-[1,10]-phenanthroline (0.132 g, 0.628 mmol) was added to NaH (60% dispersion in mineral oil) (xx mmol) in dry DMF:THF 1:1 (6.5 ml) at 0 °C. After stirring for 30 min, CH_3I (xx mmol) was added slowly and the reaction mixture was allowed to stir for 18 h at r.t before being quenched by the addition of water (5 ml). The crude mixture was extracted with DCM (30 ml x 3). The organic phase was dried over MgSO4 and concentrated *in vacuo* to afford, following reversed phase chromatography (C-18 SiO_2), the title phenanthroline compound.

6.2.22.1.1 *4,7-Di-methoxy-[1,10]-phenanthroline* (343)[112]

6.2.22.1.2 *N-Methyl-7-methoxy-[1,10]-phenanthroline-4-one* (344)



343



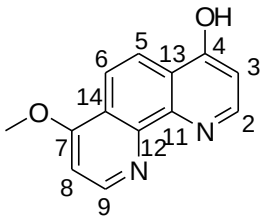
344

Following procedure **R**, CH_3I (0.09 ml, 1.38 mmol) was added to mixture of 4,7-di-hydroxy-[1,10]-phenanthroline **342** (0.132 g, 0.628 mmol) and NaH 60% (55.5 mg, 1.38 mmol) to afford 4,7-di-methoxy-[1,10]-phenanthroline **343** as a brown solid (15 mg, 10%), (mp = 206.5- 208.5 °C, lit.,[112] 210-212 °C); υ_{max} (ATR) 1588, 1566, 1505, 1419, 1350, 1313, 1287, 1249, 1056, 1020, 828, 816, 732, 672, 551, 523 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 9.0 (2H, d, *J* = 5.2 Hz, 2,9-*H*), 8.2 (2H, s, 5,6-*H*), 7.0 (2H, d, *J* = 5.2 Hz, 3,8-*H*), 4.1

(6H, s, OCH_3); δ_C (176 MHz, $CDCl_3$) 162.5 (*C*-4,7), 151.3 (*C*-2,9), 147.0 (*C*-11,12), 121.1 (*C*-13,14), 119.1 (*C*-5,6), 103.0 (*C*-3,8), 56.0 (O*C*H_3); *m/z* (LC-MS, ES^+) 240 ($[M]^+$, 100%), 241 ($[MH]^+$, 48%).

Furthermore, *N*-methyl-7-methoxy-[1,10]-phenanthroline-4-one **344** was isolated as a yellow solid (12 mg, 8%), (mp > 150 °C, decomp., lit.,[114] 190-190.5 °C); υ_{max} (ATR) 1737, 1622, 1591, 1547, 1501, 1416, 1376, 1204, 1102, 976, 932, 824, 735, 528 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.8 (1H, d, *J* = 5.1 Hz, 9-*H*), 8.5 (1H, d, *J* = 8.9 Hz, 5-*H*), 8.1 (1H, d, *J* = 8.9 Hz, 6-*H*), 7.6 (1H, d, *J* = 7.6 Hz, 2-*H*), 6.9 (1H, d, *J* = 5.1 Hz, 8-*H*), 6.5 (1H, d, *J* = 7.6 Hz, 3-*H*), 4.6 (3H, s, *N*-CH_3), 4.1 (3H, s, O-CH_3); δ_C (176 MHz, $CDCl_3$) 177.6 (*C*-4), 162.2 (*C*-7), 148.0 (*C*-9), 146.6 (*C*-2), 143.0 (*C*-12), 139.0(*C*-11), 128.2 (*C*-13), 124.0 (*C*-14), 123.1 (*C*-5), 117.4 (*C*-6), 112.3 (*C*-3), 102.1 (*C*-8), 56.1 (O*C*H_3), 49.5 (*NC*H_3); *m/z* (LC-MS, ES^+) 240 ($[M]^+$, 61%), 241 ($[MH]^+$, 100%).

6.2.22.1.3 ***4-Hydroxy-7-methoxy-[1,10]-phenanthroline*** **(345)**



Following procedure **R**, 4,7-di-hydroxy-[1,10]-phenanthroline **342** (0.628 mmol, 0.132 g), CH_3I (0.045 ml, 0.69 mmol) and NaH 60% (0.69 mmol, 27.6 mg) were combined to afford, 4-hydroxy-7-methoxy-[1,10]-phenanthroline **345** as a yellow solid (36.6 mg, 26%). m.p = 275-276 °C; υ_{max} (ATR) 3175-2838 (OH, broad, 1612, 1593, 1557, 1520, 1425, 1276, 1179, 1163, 1046, 963, 807, 798, 730, 696, 664, 552, 532, 497 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 10.5 (1H, s, O*H*), 8.7 (1H, d, *J* = 5.2 Hz, 9-*H*), 8.3 (1H, d, *J* = 9.0 Hz, 5-*H*), 8.0 (1H, d, *J* = 9.0 Hz, 6-*H*), 7.8 (1H, d, *J* = 7.4 Hz, 2-*H*), 7.0 (1H, d, *J* = 5.2 Hz, 8-*H*), 6.5

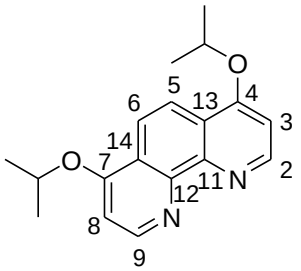
(1H, d, *J* = 7.4 Hz, 3- *H*), 4.1 (3H, s,7-OC*H*$_3$); δ_C (176 MHz, $CDCl_3$) 178.6 (*C*-4), 163.0 (*C*-7), 150.0 (*C*-9), 139.5 (*C*-12), 136.7 (*C*-11), 136.6(*C*-2), 125.2 (*C*-13), 122.2 (*C*-5), 121.9 (*C*-14), 116.3 (*C*-6), 113.3 (*C*-3), 103.1 (*C*-8), 56.2 (7-O*C*H$_3$); *m/z* (LC-MS, ES$^+$) 227 ([MH]$^+$, 100%), 475 ([M_2+Na]$^+$, 18%); HRMS (ES$^+$) found ([MH]$^+$) 227.0825; $C_{13}H_{11}N_2O_2$ requires M, 227.0821.

6.2.22.2 Procedure S:

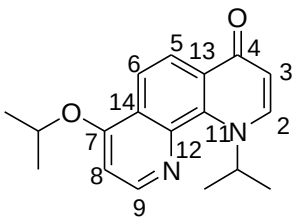
In a round bottomed flask equipped with a condenser, 2-iodopropane (xx mmol) was added to a mixture of 4,7-di-hydroxy-[1,10]-phenanthroline derivative (xx mmol) and Cs_2CO_3 (xx mmol) in dry DMF (xx ml) at 100 ^oC. The reaction mixture was heated under reflux for 6h then cooled to room temperature. The residue of Cs_2CO_3 was removed by filtration. The crude mixture was then concentrated *in vacuo* to afford, following chromatography or trituration, the title phenanthroline compound.

6.2.22.2.1 *4,7-Di-isopropoxy-[1,10]-phenanthroline* (347)

6.2.22.2.2 *N-Isopropyl-7-isopropoxy-[1,10]-phenanthroline-4-one* (349)



347



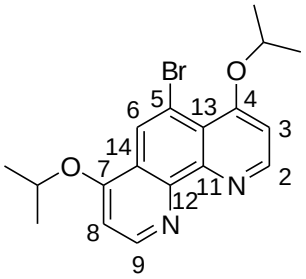
349

Following procedure **S**, 4,7-di-hydroxy-[1,10]-phenanthroline **342** (2.0 mmol, 424 mg), 2-iodopropane (0.48 ml, 2.4 eq., 4.8 mmol) and Cs_2CO_3 (3.9 g, 6.0 eq., 12.0 mmol) in dry DMF (35 ml) were heated to afford, following purification using reversed phase

chromatography (C-18 SiO_2), 4,7-di-isopropoxy-[1,10]-phenanthroline **347** as a brown solid (310 mg, 52%), (mp = 209.5-211.0 ^{O}C); υ_{max} (ATR) 1612, 1581, 1563, 1511, 1498, 1450, 1417, 1384, 1309, 1287, 1264, 1229, 1100, 1016, 961, 865, 845, 827, 807,732, 696, 628, 594, 558, 545, 518, 453, 409 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.9 (2H, d, *J* = 5.3 Hz, 2,9-*H*), 8.1 (2H, s, 5,6-*H*), 6.9 (2H, d, *J* = 5.3 Hz, 3,8-*H*), 4.7 (2H, hept, *J* = 6.1 Hz, OC*H*$(CH_3)_2$), 1.5 (12H, d, *J* = 6.1 Hz, (C*H*$_3)_4$); δ_C (176 MHz, $CDCl_3$) 161.0 (*C*-4,7), 151.0 (*C*-2,9), 147.0 (*C*-11,12), 122.0 (*C*-13,14), 119.1 (*C*-5,6), 104.1 (*C*-3,8), 71.1 (4,7-O-*C*H), 22.0 (4,7-CH(*C*$H_3)_4$); *m/z* (LC-MS, ES^+) 296 ($[M]^+$, 100%), 297 ($[MH]^+$, 73%), 615($[M_2+Na]^+$, 38%); HRMS (ES^+) found ($[MH]^+$) 297.1609; $C_{18}H_{21}N_2O_2$ requires M, 297.1603.

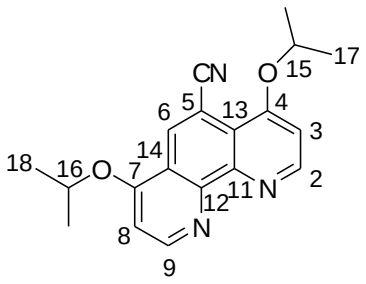
Similarly, *N*-isopropyl-7-isopropoxy-[1,10]-phenanthroline-4-one **349** was isolated as a brown oil (35 mg, 6%); υ_{max} (ATR) 1620 (C=O), 1592, 1501, 1412, 1385, 1291, 1221, 1196, 1107, 1026, 927, 820, 732, 525 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.7 (1H, d, *J* = 5.2 Hz, 9-*H*), 8.5 (1H, d, *J* = 8.9 Hz, 5-*H*), 8.1 (1H, d, *J* = 8.9 Hz, 6-*H*), 7.9 (1H, d, *J* = 7.8 Hz, 2-*H*), 7.2-7.3 (1H, m, *N*-C*H*), 6.9 (1H, d, *J* = 5.2 Hz, 8-*H*), 6.6 (1H, d, *J* = 7.8 Hz, 3-*H*), 4.8-4.9 (1H, m, O-C*H*), 1.6 (6H, d, *J* = 6.7 Hz, *N*-CH(C*H*$_3)_2$), 1.5 (6H, d, *J* = 6.0 Hz, O-CH(C*H*$_3)_2$); δ_C (176 MHz, $CDCl_3$) 177.5 (*C*-4), 161.0 (*C*-7), 148.0 (*C*-9), 143.0 (C-12), 140.0 (*C*-2), 138.5 (*C*-11), 128.5 (*C*-13), 125.0 (*C*-14), 123.0 (*C*-5), 117.5 (*C*-6), 113.0 (*C*-3), 103.0 (*C*-8), 71.0 (7-O*C*H), 55.0 (*N*-*C*H), 23.0 (*N*-CH(*C*$H_3)_2$), 22.0 (7-OCH(*C*$H_3)_2$); *m/z* (LC-MS, ES^+) 296 ($[M]^+$, 100%), 297 ($[MH]^+$, 98%), 615 ($[M_2+Na]^+$, 22%); HRMS (ES^+) found ($[MH]^+$) 297.1592; $C_{18}H_{21}N_2O_2$ requires M, 297.1603.

6.2.22.2.3 *4,7-Di-isopropoxy-5-bromo-[1,10]-phenanthroline* (350)



4-Bromo-1,2-bis-[(2,2-di-methyl-4,6-dioxo-1,3-dioxane-5-ylidenemethyl)-amino]-benzene **340** (988 mg, 2.0 mmol) was heated in di-phenyl ether, following standard procedure **Q**. The resulting product (0.42g, 1.44 mmol) was directly alkylated with 2-iodopropane (0.34 ml, 3.46 mmol) in DMF (21 ml) following general procedure **S,** to afford, following trituration with ether, 5-bromo-4,7-di-isopropoxy-[1,10]-phenanthroline **350** as a brown solid (385 mg, 51 %), (mp = 171.5-173.5 ^{o}C); υ_{max} (ATR) 1581, 1557, 1509, 1482, 1414, 1384, 1371, 1285, 1213, 1106, 1024, 959, 915, 857, 833, 601 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.9-8.8 (2H, m, 2,9-*H*, overlap), 8.4 (1H, s, 6-*H*), 7.0 (1H, d, *J* = 5.4 Hz, 3-*H*), 6.9 (1H, d, *J* = 5.4 Hz, 8-*H*), 4.88-4.83 (1H, m, 4-O-C*H*, overlap), 4.83-4.79 (1H, m, 7-O-C*H*, overlap), 1.52 (6H, d, *J* = 6.1 Hz, 4-O-CH(CH_3)$_2$), 1.47 (6H, d, *J* = 6.1 Hz, 7-O-CH(CH_3)$_2$); δ_C (176 MHz, $CDCl_3$) 161.0 (*C*-4), 160.0 (*C*-7), 151.3 (Ar-*C*), 151.0 (Ar-*C*), 148.5 (*C*-12), 146.4 (*C*-11), 125.9 (*C*-6), 121.4 (*C*-14), 119.7 (*C*-13) 113.2 (*C*-5), 105.5 (*C*-3), 104.6 (*C*-8), 72.2 (4-O-*C*H), 71.5 (7-O-*C*H), 21.81 (O-CH(*C*H_3)$_4$), 21.80 (O-CH(*C*H_3)$_4$); *m/z* (LC-MS, ES$^+$) 377 ([MH (^{81}Br)]$^+$, 96%), 375 ([MH (^{79}Br)]$^+$, 100%); HRMS (ES$^+$) found ([MH]$^+$) 375.0703; $C_{18}H_{20}{}^{80}BrN_2O_2$ requires M, 375.0708.

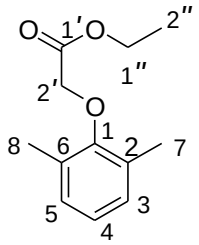
6.2.22.2.4 *4,7-Di-isopropoxy-5-cyano-[1,10]-phenanthroline* (351)



4-Cyano-1,2-bis-[(2,2-di-methyl-4,6-dioxo-1,3-dioxane-5-ylidenemethyl)-amino]-benzene **341** (882 mg, 2.0 mmol) was heated in di-phenyl ether, following standard procedure **Q**. The resulting product (441 mg, 1.86 mmol) was directly alkylated with 2-iodopropane (0.45 ml, 4.46 mmol) in DMF (25 ml) following general procedure **S,** to afford, following recrystallization from EtOAc, 5-cyano-4,7-di-isopropoxy-[1,10]-phenanthroline **351** as a brown solid (418 mg, 65 %), (mp = 207.3-208.3 ^{o}C); υ_{max} (ATR) 2220 (C*N*), 1583, 1569, 1516, 1489, 1374, 1293, 1237, 1106, 1031, 962, 829, 720, 636 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 8.92 (1H, d, *J* = 5.4 Hz, 9-*H*), 8.88 (1H, d, *J* = 5.4 Hz, 2-*H*), 8.6 (1H, s, 6-*H*), 7.0 (1H, d, *J* = 5.4 Hz, 3-*H*), 6.9 (1H, d, *J* = 5.4 Hz, 8-*H*), 4.85 (1H, hept, *J* = 6.1 Hz, 4-O-C*H*), 4.78 (1H, hept, *J* = 6.1 Hz, 7-O-C*H*), 1.5 (6H, d, *J* = 6.1 Hz, 4-O-CH(CH_3)$_2$), 1.4 (6H, d, *J* = 6.1 Hz, 7-O-CH(CH_3)$_2$); δ_C (151 MHz, $CDCl_3$) 161.0 (*C*-7), 160.0 (*C*-4), 153.8 (*C*-9), 152.0 (*C*-2), 148.0 (*C*-12), 147.0 (*C*-11), 131.0 (*C*-6), 119.8 (*C*-14), 119.2 (*5-CN*) 118.4 (*C*-13), 105.1 (*C*-3), 104.7 (*C*-8), 103.8 (*C*-5), 72.7 (4-O-*C*H), 71.8 (7-O-*C*H), 21.6 (O-CH(*C*H_3)$_2$), 21.3 (O-CH(*C*H_3)$_2$); *m/z* (LC-MS, ES$^+$) 322 ([MH]$^+$, 96%), 321 ([M]$^+$, 89%), 665 ([M_2+Na]$^+$, 38%); HRMS (ES$^+$) found ([MH]$^+$) 322.1563; $C_{19}H_{20}N_3O_2$ requires M, 322.1556.

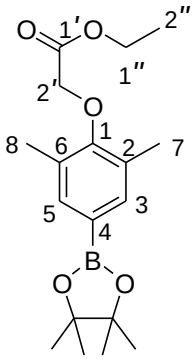
6.2.23 *Borylation of (2,6-di-methyl-phenoxy)-acetic acid ethyl ester*

6.2.23.1 *Preparation of (2,6-di-methyl-phenoxy)-acetic acid ethyl ester (353)*[146]



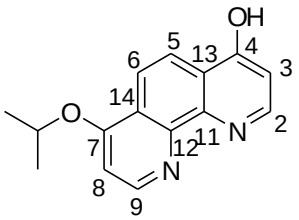
In a round bottom flask, equipped with a condenser, 2,6-di-methylphenol **352** (0.49 g, 4 mmol) and potassium carbonate (0.66 g, 4.8 mmol) in acetone (20 ml) were refluxed at 80 ^{o}C for 15 min, ethyl bromoacetate (0.67 ml, 6 mmol) was then added dropwise. The reaction mixture was heated under reflux overnight before cooling to r.t. The solvent residue was removed *in vacuo* to afford, following chromatography (hexane:EtOAc 9:1), (2,6-di-methylphenoxy)acetic acid ethyl ester **353** as a yellow oil (0.8 g, 96%); υ_{max} (ATR) 1760 (C=O ester), 1476, 1379, 1263, 1185, 1094, 1068, 1031, 768 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 7.03-6.98 (2H, m, 3,5-*H*), 6.9 (1H, m, 4-*H*), 4.4 (2H, s, 2'-*H*), 4.3 (2H, q, *J* = 7.1 Hz, 1"-*H*), 2.35 (6H, s, 2,6-(C*H*$_3$)$_2$), 1.33 (3H, t, *J* = 7.1 Hz, 2"-*H*); δ_C (176 MHz, $CDCl_3$) 169.2 (*C*=O), 155.4 (*C*-1), 130.7 (*C*-2), 129.0 (*C*-3), 124.5 (*C*-4), 69.2 (*C*-2'), 61.2 (*C*-1"), 16.3 (2,6-(*C*H$_3$)$_2$), 14.3 (*C*-2"); *m/z* (GC-MS, EI$^+$) 208 ([M]$^+$, 40%), 162 found, 135 ([M-$C_3H_5O_2$]$^+$, 41%), 121 ([M-$C_4H_7O_2$]$^+$, 100%), 105 ([M-$C_4H_7O_3$]$^+$, 41%) .

6.2.23.2 *Preparation of [2,6-di-methyl-4-(4,4,5,5-tetra-methyl-[1,3,2]-diox-aborolan-2-yl)-phenoxy]-acetic acid ethyl ester* (354)



$[Ir(OMe)cod]_2$ (0.02 g, 0.03 mmol, 3.0 mol%), dtbpy (16 mg, 0.06 mmol, 6.0 mol%,) and B_2pin_2 (1.5 mmol, 381 mg) and (2,6-di-methyl-phenoxy)-acetic acid ethyl ester **353** (0.21 g, 1.0 mmol) were placed in the vessel which was then sealed, evacuated, backfilled with N_2 and THF (8 ml) was then added. The reaction mixture was heated in oil bath at 80 ^oC for 4 h. The reaction mixture was cooled to r.t and concentrated *in vacuo* to afford, following chromatography (hexane:EtOAc 9:1), [2,6-di-methyl-4-(4,4,5,5-tetra-methyl-[1,3,2]-dioxaborolan-2-yl)phenoxy]-acetic acid ethyl ester **354** as a white colorless oil (186 mg, 56 %); υ_{max} (ATR) 2979, 1761, 1603, 1366, 1312, 1184, 1141, 1069, 966, 853, 736, 687 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 7.5 (2H, d, *J* = 1.3 Hz, 3,5-*H*), 4.4 (2H, s, 2'-*H*), 4.3 (2H, q, *J* = 7.1 Hz, 1"-H), 2.3 (6H, s, 2,6-(CH_3)$_2$), 1.35-1.25 (15H, m, 2"-*H*,,OC(CH_3)$_4$); δ_C (176 MHz, $CDCl_3$) 168.9 (*C*=O), 158.1 (*C*-1), 135.8 (*C*-3), 130.0 (*C*-2), 83.7 (O*C*-(CH_3)$_4$), 69.2 (*C*-2'), 61.2 (*C*-1"), 24.8 (OC-(*C*H_3)$_4$), 16.1 (2,6-(*C*H_3)$_2$), 14.2 (*C*-2"), unobserved (*C*-4); *m/z* (GC-MS, EI^+) 334 ([M]$^+$, 100%), 319 ([M-CH_3]$^+$, 20%), 261 ([M-$C_3H_5O_2$]$^+$, 25%), 247 ([M-$C_4H_7O_2$]$^+$, 72%).

6.2.24 *4-Hydroxy-7-isopropoxy-[1,10]-phenanthroline* (348)



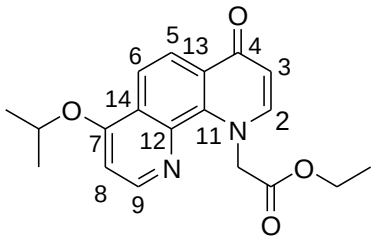
Following procedure **S** in section **6.2.22.2,** 2-iodopropane (0.24 ml, 2.4 mmol) was added portionwise to a mixture of 4,7-di-hydroxy-[1,10]-phenanthroline **342** (2.0 mmol, 424 mg) and Cs_2CO_3 (1.95 g, 6.0 mmol) in dry DMF (35 ml) at 100 ^oC. The reaction mixture was concentrated *in vacuo* to remove solvent. The resulting crude mixture was then re-dissolved in DCM, filtrated and washed with DCM. The solid residue was dissolved in H_2O (20 ml) before adding 3 M HCl until the pH reached 7. The resulting brown solid was filtered and dried *in vacuo* to recover 4,7-di-hydroxy-[1,10]-phenanthroline **342** (0.5 mmol). The DCM filtrate was concentrated *in vacuo* to afford a white solid, which was purified using reversed phase chromatography C18-SiO_2 or dissolving the resulting crude mixture with EtOAc (50 ml) and washing with 10% NaOH (aq.) (3 x 30 ml). The aqueous solution was then neutralised with HCl (pH = 7) and extracted with EtOAc (2 x 30 ml). The organic layer was then concentrated *in vacuo*, dissolved in H_2O and washed with $NaHCO_3$ (aq.) to remove the resulting acetic acid, then extracted with DCM (50 ml). The organic phase was dried over MgSO4 and filtered. The solvent was removed *in vacuo* to afford, 4-hydroxy-7-isopropoxy-[1,10]-phenanthroline **348** as an off white solid (230 mg, 45%), (mp = 205.5-206 ^oC); υ_{max} (ATR) 3301-2827 (OH broad), 1623, 1586, 1554, 1512, 1425, 1280, 1239, 1186, 1167, 1108, 1010, 939, 835, 822, 738, 670, 530, 463 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 10.8 (1H, s, O*H*), 8.6 (1H, d, *J* = 5.3 Hz, 9-*H*), 8. 3 (1H, d, *J* = 9.0 Hz, 5-*H*), 8.0 (1H, d, *J* = 9.0 Hz, 6-*H*), 7.8 (1H, d, *J* = 7.3 Hz, 2-*H*), 6.9 (1H, d, *J* = 5.3 Hz, 8-*H*), 6.5 (1H, d, *J* = 7.3 Hz, 3-*H*), 4.8

(1H, hept, *J* = 6.1 Hz, 7-OC*H*$(CH_3)_2$), 1.5 (6H, d, *J* = 6.1 Hz, 7-OCH(C*H*$_3)_2$); δ_C (176 MHz, $CDCl_3$) 178.7 (*C*-4), 161.1 (*C*-7), 150.1 (C-9), 140.3 (C-12), 136.9 (C-11), 136.7(*C*-2), 125.1 (*C*-13), 122.4 (*C*-14), 121.7 (*C*-5) 116.6 (*C*-6), 113.1 (*C*-3), 104.3 (*C*-8), 71.5 (7-O*C*$H(CH_3)_2$), 21.8 (7-OCH(*C*$H_3)_2$); *m/z* (LC-MS, ES^+) 254 ($[M]^+$, 75%), 255 ($[MH]^+$, 100%), 509 ($[M_2H]^+$, 13%); HRMS (ES^+) found ($[MH]^+$) 255.1131; $C_{15}H_{15}N_2O_2$ requires M, 255.1134.

6.2.25 General procedure T: Alkylation of 4-hyroxy-7-isopropyl-[1,10]-phenanthroline

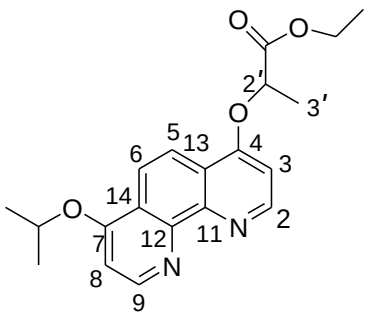
In a round bottom flask, equipped with a condenser, 4-hydroxy-7-isopropyl-[1,10]-phenanthroline (1.0 mmol, 254 mg), cesium carbonate (3.0 mmol, 0.98 g) and Bu_4NI (10 mol%, 0.2 mmol, 73.9 mg) in DMF (15 ml) were heated at the stated temperature, alkyl bromide (X mmole) was then added dropwise. The reaction mixture were allowed to heat at the stated temprature for 17 h then cooled to r.t. The residue of Cs_2CO_3 was removed by filtration and the solvent was then concentrated under reduce pressure to afford, following chromatography or recrystallization from EtOAc, the desired product.

6.2.25.1 *(7-Isopropoxy-4-oxo-4H-[1,10]-phenanthrolin-1-yl)-acetic acid ethyl ester* (370)



Following procedure **T**, 4-hydroxy-7-isopropyl-[1,10]-phenanthroline **348** and ethyl bromoacetate (0.22 ml, 2 mmol) were combined at 100 ^{o}C to afford, following chromatography (MeOH:DCM 1.0:14), (7-isopropoxy-4-oxo-4H-[1,10]-phenanthrolin-1-yl)-acetic acid ethyl ester **370** as a yellow color solid (70 mg, 21 %), (mp > 160 ^{o}C, decomp.); υ_{max} (ATR) 1739, 1623, 1587, 1549, 1501, 1416, 1377, 1278, 1199, 1173, 1111, 1028, 982, 824, 734, 529 cm^{-1}, δ_H (600 MHz, $CDCl_3$) 8.6 (1H, d, *J* = 5.2 Hz, 9-*H*), 8.4 (1H, d, *J* = 9.0 Hz, 5-*H*), 8.1 (1H, d, *J* = 9.0 Hz, 6-*H*), 7.5 (1*H*, d, *J* = 7.7 Hz, 2-*H*), 6.8 (1H, d, *J* = 5.2 Hz, 8-*H*), 6.5 (1H, d, *J* = 7.7 Hz, 3-*H*), 5.5 (2H, s, *N*-C*H*$_2$), 4.8 (1H, hept, *J* = 6.1 Hz, 7-OC*H*$(CH_3)_2$), 4.2 (2H, q, *J* = 7.1 Hz, OC*H*$_2$-CH_3), 1.5 (6H, d, *J* = 6.1 Hz, 7-OCH(C*H*$_3)_2$), 1.2 (3H, t, J = 7.1 Hz, OCH_2-C*H*$_3$); δ_C (151 MHz, $CDCl_3$) 177.7 (*C*-4), 168.8 (*C*=O, ester), 160.6 (*C*-7), 147.5 (*C*-9), 146.4 (*C*-2), 142.0 (*C*-12), 137.6 (*C*-11), 127.7 (*C*-13), 124.3 (*C*-14), 122.6 (*C*-5), 117.8 (*C*-6), 112.7 (*C*-3), 103.3 (*C*-8), 71.3 (7-O*C*H$(CH_3)_2$), 61.4 (O*C*H$_2$-CH_3), 61.2 (*N*-*C*H$_2$), 21.7 (7-OCH(*C*H$_3)_2$), 14.3 (OCH_2-*C*H$_3$); *m/z* (LC-MS, ES$^+$) 681 ([M+H]$^+$, 82%), 341 ([MH]$^+$, 63%), 340 ([M]$^+$, 100%); HRMS (ES$^+$) found ([MH]$^+$) 341.1498; $C_{19}H_{20}N_2O_4$ requires M, 341.1501

6.2.25.2 ***2-(7-Isopropoxy-[1,10]-phenanthrolin-4-yloxy)-propionic acid ethyl ester*** **(367)**



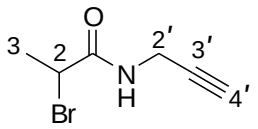
Following procedure **T**, 4-hydroxy-7-isopropyl-[1,10]-phenanthroline **348** and ethyl-2-bromopropinoate (0.26 ml, 2 mmol) were combined at 100 ^{o}C to afford, following reversed phase chromatography (C18-SiO_2), 2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-propionic acid ethyl ester **367** as a white color solid (0.23 g, 65 %), (mp = 153-154 ^{o}C); υ_{max} (ATR) 1733 (C=O), 1585, 1564, 1509, 1498, 1446, 1418, 1307, 1285, 1260, 1229, 1186, 1093, 1049, 999, 956, 824, 739, 700, 450 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.91-8.88 (2H, m, 2,9-*H*), 8.18-8.12 (2H, m, 5,6-*H*), 6.9 (1H, d, *J* = 5.2 Hz, 8-*H*), 6. 75 (1H, d, *J* = 5.2 Hz, 3-*H*), 4.9 (1H, q, *J* = 6.8 Hz, 2'-*H*), 4.8 (1H, hept, *J* = 6.1 Hz, 7-OC*H*$(CH_3)_2$), 4.17 (2H, q, *J* = 7.2 Hz, O-CH_2), 1.74 (3H, d, *J* = 6.8 Hz, 3'-*H*), 1.4 (6H, d, *J* = 6.1 Hz, 7-OCH(C$H_3)_2$), 1.16 (3H, t, *J* =7.2 Hz, CH_3); δ_C (176 MHz, $CDCl_3$) 170.9 (*C*=O), 160.6 (*C*-7), 160.3 (*C*-4), 151.0 (Ar-*C*), 150.6 (Ar-*C*), 147.2 (*C*-11), 147.0 (*C*-12), 121.6 (*C*-14), 120.9 (*C*-13), 119.5 (Ar-*C*) 118.7 (Ar-*C*), 104.1 (*C*-8), 103.7 (*C*-3), 73.0 (*C*-2'), 71.0 (7-O*C*H$(CH_3)_2$), 61.6 (O-*C*H_3), 21.7 (7-OCH(*C*$H_3)_2$), 18.3 (*C*-3'), 14.0 (*C*H_3); *m/z* (LC-MS, ES^+) 354 ($[M]^+$, 100), 731 ($[M_2Na]^+$); HRMS (ES^+) found ($[MH]^+$) 355.1666, $C_{20}H_{23}N_2O_4$ requires M, 355.1658; CHN found C% 67.62, H% 6.26, N% 7.74; $C_{20}H_{22}N_2O_4$ required C% 67.78, H% 6.26, N% 7.9.

6.2.26 Coupling of primary amine with carboxylic acid

6.2.26.1 General procedure U

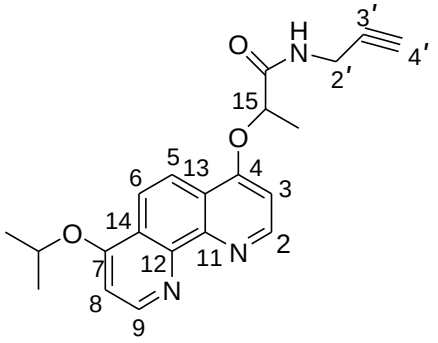
In a round bottomed flask, acyl chloride (2.0 mmol) was added dropwise to a mixture of primary amine derivatives (2.0 mmol) and base (2.4 mmol) in dry DCM (10 ml) at 0 ^{o}C. The reaction mixture was then allowed to stir for 17 h to afford, following chromatography or trituration, the title amide compound.

6.2.26.1.1. *2-Bromo-N-(prop-2-yn-1-yl)-propanamide* (378)[147]



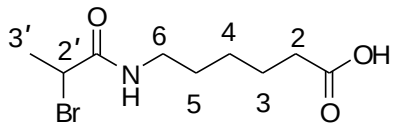
2-Bromo-propionyl chloride **376** (0.2 ml, 2.0 mmol) and propargylamine **377** (0.13 ml, 2.0 mmol) were combined following standard procedure **S** using tri-ethyamine (0.3 ml, 2.4 mmol) as base in DCM (10 ml) to afford, following chromatography (EtOAc:hexane 3:8), 2-bromo-*N*-(prop-2-yn-1-yl)-propanamide **378** as a yellow solid (335 mg, 88%), (mp = 53-54 ^{o}C); υ_{max} (ATR) 3279 (≡-H), 3063 (*N*H, amide), 1645 (C=O, amide), 1539, 1444, 1373, 1334, 1249, 1189, 1076, 1053, 1008, 975, 654, 512 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 7.35 (1H, s broad, *N*-*H*), 4.43 (1H, q, *J* = 7.0 Hz, 2-*H*), 4.05-3.94 (2H, m, 2'-*H*), 2.23 (1H, t, *J* = 2.6 Hz, 4'-*H*), 1.77 (3H, d, *J* = 7.0 Hz, 3-*H*); δ_C (176 MHz, $CDCl_3$) 169.7 (*C*=O), 78.9 (*C*-3'), 71.86 (*C*-4'), 43.6 (*C*-2), 29.8 (*C*-2'), 22.4 (*C*-3); *m/z* (LC-MS, EI$^+$) 191 ([M (^{81}Br)]$^+$, 100%), 189 ([M (^{79}Br)]$^+$, 92%); HRMS (ES$^+$) found ([MH]$^+$) 189.9883; $C_6H_9{}^{79}BrNO$ requires M, 189.9868.

6.2.27 *2-(7-Isopropoxy-[1,10]-phenanthrolin-4-yloxy)-N-prop-2-ynyl-propionamide* (379)



Following procedure **T**, 4-hydroxy-7-isopropyl-[1,10]-phenanthroline **348** and 2-bromo-N-(prop-2-yn-1-yl)-propanamide **378** (254 mg, 1.0 mmol) were combined at r.t to afford, following recrystallization from EtOAc, 2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-N-prop-2-ynyl-propionamide **379** as an off-white solid (60 mg, 17 %), (mp = > 200 ^{o}C decomp.); υ_{max} (ATR) 3336 (Alkyne), 1662, 1585, 1569. 1508, 1423, 1309, 1281, 1228, 1089, 995, 953, 818, 730, 628 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.93 (1H, d, *J* = 5.2 Hz, 9-*H*), 8.86 (1H, d, *J* = 5.2 Hz, 2-*H*), 8.1 (1H, d, *J* = 9.2 Hz, 6-*H*), 7.9 (1H, d, *J* = 9.2 Hz, 5-*H*), 7.22 (1H, s, N*H*, broad), 7.0 (1H, d, *J* = 5.2 Hz, 8-*H*), 6.9 (1H, d, *J* = 5.2 Hz, 3-*H*), 5.0 (1H, q, *J* = 6.7 Hz, 15-*H*), 4.9 (1H, hept, *J* = 6.1 Hz, 7-OC*H*$(CH_3)_2$), 4.19-4.08 (2H, m, *N*H-C*H*$_2$), 2.18 (1H, t, J = 2.5 Hz, 4'-*H*), 1.8 (3H, d, *J* = 6.7 Hz, 15-C*H*$_3$), 1.54 (3H, d*, J* = 6.1 Hz, 7-OCH(C*H*$_3)_2$), 1.51 (3H, d*, J* = 6.1 Hz, 7-OCH(C*H*$_3)_2$); δ_C (176 MHz, $CDCl_3$) 170.8 (*C*=O), 160.8 (*C*-7), 159.5 (*C*-4), 151.2 (*C*-9), 150.9 (*C*-2), 147.1 (*C*-11), 147.0 (*C*-12), 121.7 (*C*-14), 120.7 (*C*-13), 120.0 (*C*-6) 118.0 (*C*-5), 104.5 (*C*-3), 104.4 (*C*-8), 79.0 (*C*-3'), 75.6 (*C*-15), 71.7 (*C*-4'), 71.3 (7-O*C*H$(CH_3)_2$), 29.0 (*N*H-*C*H$_2$), 21.94 (7-OCH(*C*H$_3)_2$), 21.92 (7-OCH(*C*H$_3)_2$), 18.8 (15-*C*H$_3$); *m/z* (LC-MS, ES^+) 364 ($[MH]^+$, 100%), 749 ($[M_2Na]^+$, 20%); HRMS (ES^+) found ($[MH]^+$) 364.1655; $C_{21}H_{22}N_3O_3$ requires M, 364.1661.

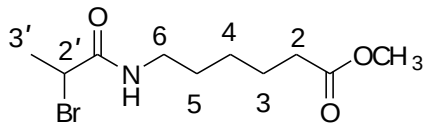
6.2.28 *6-(2-Bromo-propionylamino)-hexanoic acid* (381)



2-Bromo-propionyl chloride **376** (0.2 ml, 2.0 mmol) and 6-aminocaproic acid **380** (262 mg, 2.0 mmol) were combined following standard procedure **U** using potassium carbonate (332 mg, 2.4 mmol) as base. 40 ml of H_2O was added to the reaction

mixture. The aqueous phase was separated and washed with DCM (10 ml). HCl was added to the aqueous solution to make (PH=2-3) then extracted with EtOAc (20 ml x 3). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo* to afford, following trituration with ether, 6-(2-bromo-propionylamino)-hexanoic acid **381** as a white solid (0.23 g, 43 %), (mp = 89.8-90.8 ^oC); υ_{max} (ATR) 3277 (*N*H), 1700 (C=O, acid), 1652 (C=O, amide),1569, 1429, 1250, 1197, 1070, 980, 899, 594, 489 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 10.4 (1H, s, O*H*), 6.6 (1H, s, *NH*), 4.4 (1H, q, *J* = 7.0 Hz, 2'-*H*), 3.26 (2H, d, *J* = 6.8 Hz, 6-*H*), 2.3 (2H, t, *J* = 7.4 Hz, 2-*H*), 1.8 (3H, d, *J* = 7.0 Hz, 3'-*H*), 1.66-1.6 (2H, m, 3-*H*), 1.57-1.51 (2H, m, 5-*H*), 1.39-1.33 (2H, m, 4-*H*); δ_C (176 MHz, $CDCl_3$) 174.0 (*C*=O carboxylic acid), 169.7 (*C*=O amide), 45.3 (*C*-2'), 40.0 (*C*-6), 34.0 (*C*-2), 29.0 (*C*-5), 26.2 (*C-4*), 24.3 (*C-3*), 23.2 (*C-3*'); *m/z* (LC-MS, EI^-) 266 ([M (^{81}Br)-H]$^-$, 100%), 264 ([M (^{79}Br)-H]$^-$, 100%); HRMS (ES^+) found ([M-H]$^-$) 264.0227; $C_9H_{15}{}^{79}BrNO_3$ requires M, 264.0235.

6.2.29 *6-(2-Bromo-propionylamino)-hexanoic acid methyl ester* (383)

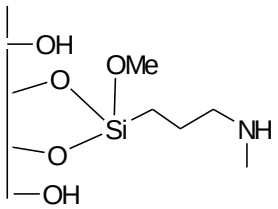


In a round bottomed flask, TMS-diazomethan solution in 2 M hexane (1.8 mmol, 0.9 ml) was added dropwise under N_2 to 6-(2-bromo-propionylamino)-hexanoic acid **381** (0,25 mmol, 532 mg) in mixture of MeOH:EtOAc 1:1 (10 ml) at 0 ^0C. The reaction mixture was then allowed to stir at room temperature overnight. The solvent was removed *in vacuo* and the resultant crude mixture re-dissolved in DCM (30 ml), washed (aq. $NaHCO_3$), dried over $MgSO_4$ and concentrated to afford, without further purification, 6-(2-Bromo-propionylamino)-hexanoic acid methyl ester **383** as a white oil (0.5 g, 89%); υ_{max} (ATR) 3273 (*N*H, amide), 1734 (C=O, ester), 1647 (C=O, amide), 1557,

1431, 1370, 1302, 1237, 1190, 1172, 982, 882, 729 cm^{-1} δ_H; (700 MHz, $CDCl_3$) 6.9 (1H, *t*, *J* = 5.8 Hz, *NH*), 4.3 (1H, q, *J* = 6.9 Hz, 2'-*H*), 3.5 (3H, s, OCH_3), 3.14 (2H, m, 6-*H*), 2.2 (2H, t, *J* = 7.5 Hz, 2-*H*), 1.7 (3H, d, *J* = 6.9 Hz, 3'-*H*), 1.56-1.48 (2H, m, 3-*H*), 1.43 (2H, pent, *J* = 7.2 Hz, 5-*H*), 1.3-1.2 (2H, m, 4-*H*); δ_C (176 MHz, $CDCl_3$) 173.8 (*C*=O ester), 169.5 (*C*=O amide), 51.3 (OCH_3), 44.4 (*C*-2'), 39.6 (*C*-6), 33.7 (*C*-2), 28.7 (*C*-5), 26.1 (*C-4*), 24.3 (*C-3*), 22.5 (*C-3*'); *m/z* (LC-MS, EI^+) 585 ([M_2 (^{81}Br)+Na]$^+$, 10%), 582 ([M_2H (^{79}Br)+Na]$^+$, 19%), 282 ([MH (^{81}Br)]$^+$, 80%), 280 ([MH (^{79}Br)]$^+$, 100%); HRMS (ES^+) found ([M-H]$^-$) 280.0554; $C_{10}H_{19}{}^{79}BrNO_3$ requires M, 280.0548.

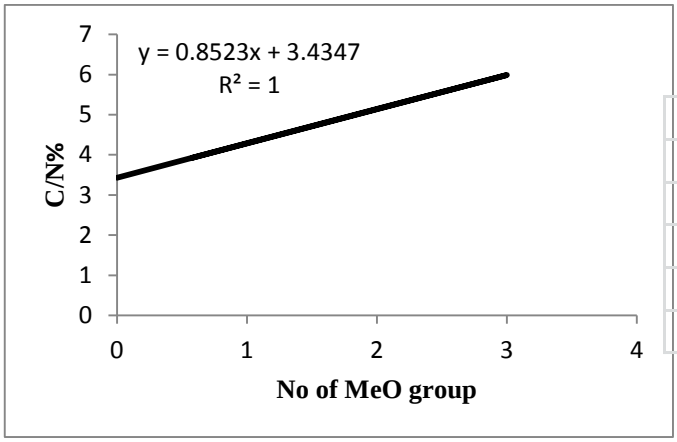
6.2.30 Preparation of silica supported iridium catalysis

6.2.30.1 *Grafting the N-methylaminopropyltri-ethoxysilane onto MCM-41* (386)



In a 25 ml microwave vessel, following Yuan's procedure,[121] MCM-41 (0.8 g) was dehydrated *in vacuo* at 200 °C for 2 h before adding dry toluene (15 ml) under nitrogen. *N*-methylaminopropyltri-methoxysilane **373** (1.1 ml, 5.56 mmol) was added portionwise to the reaction vessel. The reaction mixture was heated at 120 °C for 35 h, then cooled and filtered *in vacuo* and the resulting solid washed with dry toluene, MeOH, then dried *in vacuo* overnight at 60 °C to afford the (MCM-41) **386** as a white solid (0.95 gm, 1.21 mmol/g polymer); υ_{max} (ATR) 1050, 1614, 844, 800, 438 cm^{-1}; δ_C

VNMRS CP (100.562 MHz) 50 (NCH_2, $SiOCH_3$), 34 (NCH_3), 22 (CH_2), 10 ($SiCH_2$); CHN found C% 10.58, H% 2.65, N% 2.70; $C_5H_{13}NOSi$ required C% 45.76, H% 9.98, N% 10.67.

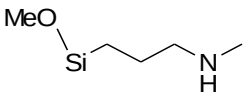


No MeO	(C/N)%
0	3.43
1	4.29
2	5.146
3	5.986
0.577	3.927

Weight of MCM-41= 0.8 g; weight of the resulting polymer= 0.95 g

Grafting the N-methylpropyltri-methoxysilane onto MCM-41= 0.15 g

Depending on the percentage of C/N with the number of methoxy group in CHN analysis

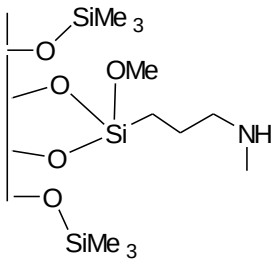


Molecular weight = 131

mmol/ 0.95 g= 0.15/131= 1.145

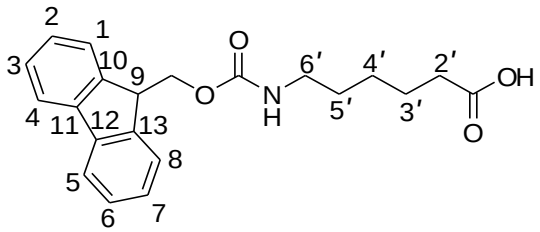
mmol/ g= 1.205

6.2.30.2 *End-Capping the functionalized MCM-41* (387)



In a 25 ml microwave vessel, a mixture of polymer **386** (1.0 gm) and HMDS (6 ml, 28.6 mmol) in dry toluene (15 ml) was stirred at room temperature overnight. The resulting solid washed by dry toluene, hexane and DCM, then dried *in vacuo* overnight at 60 ^{o}C to afford (MCM-41) **387** as a white solid (1.054 gm, 1.14 mmol/g); δ_C VNMRS CP (100.562 MHz) 50 (*N*CH_2, SiOCH_3), 34 (*N*CH_3), 22 (CH_2), 10 (SiCH_2), 0.0 (Si$(CH_3)_3$) .

6.2.31 *6-(9H-Fluoren-9-ylmethoxycarbonylamino)-hexanoicacid* (389)[127]



In round bottomed flask, 6-amino caproic acid **380** (656 mg, 5.0 mmol) and Na_2CO_3 (1.59 g, 15.0 mmol) in a mixture of dioxane:H_2O 1:1 (16 ml) were stirred at 0 ^{o}C for 10 min. Fmoc-Cl **388** (1.3 g, 5.0 mmol) was then added portionwise to the reaction mixture . The reaction mixture was allowed to warm to r.t and stirred for further 6 h. 50 ml of H_2O was added to the reaction mixture before adding 3 M HCl until the pH reached 5-6. The resulting precipitate was then filtrated *in vacuo* to afford, following washing with H_2O and hexane, chromatography (MeOH:DCM 1:9), 6-(9H-fluoren-9-ylmethoxycarbonylamino)-hexanoic acid **389** as a white solid (1.53 g, 87%), (mp = 118.5 – 119.5 ^{o}C); υ_{max} (ATR) 3339 (*N*H, OH), 1687 (C=O, carbamate, acid), 1530, 1269,

1253, 1237, 1130, 1102, 995, 758, 735, 621, 577, 528, 427 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 7.8 (2H, d, *J* = 7.6 Hz, 4,5-*H*), 7.6 (2H, d, *J* = 7.7 Hz, 1,8-*H*), 7.4 (2H, t, *J* = 7.5 Hz, 3,6-*H*), 7.3 (2H, t, *J* = 7.5 Hz, 2,7-*H*), 6.1 (0.3H, s, *NH* rotamer A), 4.9 (0.7H, s, *NH* rotamer B), 4.52-4.45 (0.7H, m, O-C*H*$_2$, rotamer A), 4.4 (1.3H, d, *J* = 7.0 Hz, O-C*H*$_2$, rotamer B), 4.23 (1H, m, 9-*H*, rotamers A and B), 3.2 (1.4H, q, *J* = 6.6 Hz, 6'-*H*, rotamer B), 3.1 (0.6H, q, *J* = 6.6 Hz, 6'-*H*, rotamer A), 2.4 (2H, t, *J* = 7.5 Hz, 2'-*H*), 1.6 (2H, m, 3'-*H*, rotamers A and B), 1.5 (1.4H, m, 5'-*H*, rotamer B), 1.38-1.33 (0.6H, m, 5'-*H*, rotamer A), (1.3H, m, 4'-*H*, rotamer A), 1.3 (0.7H, m, 4'-*H*, rotamer B); δ_C (176 MHz, $CDCl_3$) 179.2 (*C*=O carboxylic acid, rotamers A and B), 157.9 (*C*=O amide, rotamer A), 156.6 (*C*=O amide, rotamer B), 144.0 (*C*-10, 13, rotamers A and B), 141.3 (*C*-11, 12), 127.7 (*C*-3,6), 127.1 (*C*-2,7), 125.1 (*C*-1,8, rotamers A and B), 120.0 (*C*-4,5), 67.2 (O*C*H$_2$, rotamer A), 66.6 (O*C*H$_2$, rotamer B), 47.3 (*C*-9, rotamers A and B), 41.4 (*C*-6', rotamer A), 40.8 (*C*-6', rotamer B), 34.0 (*C*-2', rotamers A and B), 29.6 (*C*-5', rotamers A and B), 26.2 (*C*-4', rotamers A and B), 24.3 (*C*-3', rotamers A and B); *m/z* (LC-MS, EI^-) 705 ($[M_2\text{-}H]^-$, 100%), 352 ($[M\text{-}H]^-$, 16%).

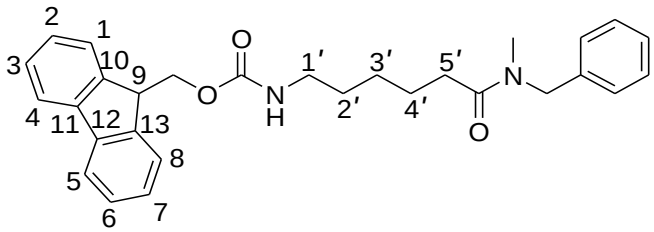
6.2.32 <u>The coupling of sec amine with carboxylic acid</u>

Under N_2, in a round bottomed flask, EDCI (X mmol) was dissolved in dry DCM (X ml), and solution was cooled to 0 ^oC before carboxylic acid (X mmol) was added. The reaction mixture was allowed to stir at 0 ^oC for 1.5 h. DMAP (X mmol), DIPEA (X mmol) and sec amine (X mmol) were then added to the reaction mixture. The reaction mixture was allowed to warm to room temperature and allowed to stir overnight. The reaction mixture was worked up and purification carried out by the stated method.

Protocol V1: The reaction mixture was quenched by addition of NH_2Cl (aq.) and extracted with EtOAc (2 x 20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to afford, following chromatography (MeOH:DCM 1.0:12), the title amide compound.

Protocol V2: The reaction mixture was filtered *in vacuo*, and then washed with dry DMF, DCM and MeOH. The resulting solid was dried *in vacuo* at 65^0C overnight to afford the title amid compound.

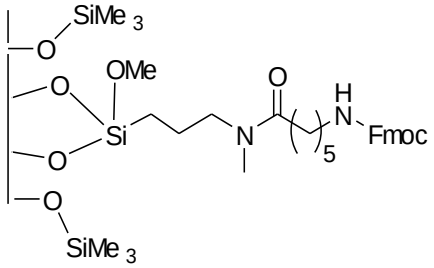
6.2.32.1 *[5-(Benzyl-methyl-carbamoyl)-pentyl]-carbamic acid 9H-fluoren-9-ylmethyl ester* (393)



Following procedure **V1**, EDCI (0.66 mmol, 126.5 mg) in DCM (5 ml), 6-(9H-fluoren-9-ylmethoxycarbonylamino)-hexanoic acid **389** (0.3 mmol, 106 mg), DMAP (0.12 mmol, 14.7 mg), DIPEA (0.75 mmol, 0.13 ml) and *N*-benzylmethylamine **392** (0.6 mmol, 0.08 ml) were coupled at room temperature to afford the [5-(benzyl-methyl-carbamoyl)-pentyl]-carbamic acid 9H-fluoren-9-ylmethyl ester **393** as a clear oil (37.5 mg, 27%); υ_{max} (ATR) 3311 (*N*H broad), 1700 (C=O, carbamate), 1627 (C=O, amide), 1533, 1450, 1244, 1135, 759, 738, 697, 621, 426 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 7.8 (2H, d, *J* = 7.6 Hz, 4,5-*H*), 7.6 (2H, d, *J* = 7.5 Hz, 1,8-*H*), 7.42-7.21 (8H, m, 2,3,6,7-*H* and Ar-*H*), 7.1 (1H, d, *J* = 7.5 Hz, Ar-*H*), 5.0 (1H, m, *NH* rotamers A and B), 4.6 (1.2H, s, Ar-CH_2, rotamer A), 4.5 (0.8H, s, Ar-CH_2, rotamer B), 4.4 (2H, m, O-CH_2, rotamers A and B), 4.2 (1H, t, *J* = 7.1 Hz,

9-*H*, rotamers A and B), 3.25-3.15 (2H, m, 1'-*H*, rotamers A and B), 3.0 (1.3H, s, *NCH*$_3$, rotamer B), 2.9 (1.7H, s, *NCH*$_3$, rotamer A), 2.41-2.32 (2H, m, 5'-*H*, rotamers A and B), 1.75-1.65 (2H, m, 4'-*H*, rotamers A and B), 1.6 (1.0H, m, 2'-*H*, rotamer A), 1.5 (1.0H, m, 2'-*H*, rotamer B), 1.40 (1.0H, m, 3'-*H*, rotamer A), 1.34 (1.0H, m, 3'-*H*, rotamer B); δ_C (151 MHz, $CDCl_3$) 173.4 (*C*=O amid, rotamer A), 173.0 (*C*=O amid, rotamer B), 156.6 (*C*=O carbamate, rotamers A and B), 144.1 (*C*-10,13), 141.4 (*C*-11, 12), 137.6 (Ar-C*H*$_2$, rotamer A), 136.8 (Ar-C*H*$_2$, rotamer B), 129.0 (Ar-*C*), 128.7 (Ar-*C*), 128.1 (Ar-*C*), 127.7 (Ar-*C*), 127.1 (Ar-*C*), 126.3 (Ar-*C*), 125.2 (*C*-1,8), 120.0 (*C*-4,5), 67.0 (OC*H*$_2$, rotamer A), 66.6 (OC*H*$_2$, rotamer B), 53.4 (Ar-C*H*$_2$, rotamer B), 50.9 (Ar-C*H*$_2$, rotamer A), 47.4 (*C*-9, rotamer A and B), 40.9 (*C*-1', rotamer A), 40.8 (*C*-1', rotamer B), 34.9 (*NC*H$_3$, rotamer A), 34.1 (*NC*H$_3$, rotamer B), 33.4 (*C*-5', rotamer A), 32.9 (*C*-5', rotamer B), 29.8 (*C*-2', rotamer A), 29.7 (*C*-2', rotamer B), 26.6 (*C*-3', rotamer A), 26.5 (*C*-3', rotamer B), 24.8 (*C*-4', rotamer A), 24.6 (*C*-4', rotamer B); *m/z* (LC-MS, EI$^+$) 936 ([M$_2$H+Na]$^+$, 100%), 457 ([MH]$^+$, 56%); HRMS (ES$^+$) found ([MH]$^+$) 257.2484; $C_{29}H_{33}N_2O_3$ requires M, 257.2491.

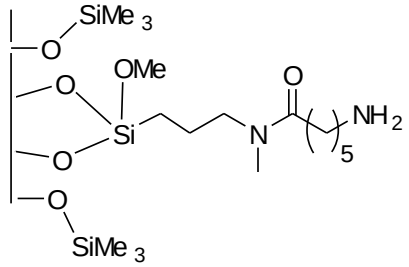
6.2.32.2 ***Immobilisation of Fmoc onto MCM-41*** **(390)**



Following procedure **V2**, EDCI (7.52 mmol, 1.44 gm) in DCM (45 ml), 6-(9H-fluoren-9-ylmethoxycarbonylamino)-hexanoic acid **389** (1.21 gm, 3.42 mmol), DMAP (167 mg, 1.37 mmol), DIPEA (1.5 ml, 8.55 mmol) and (MCM-41) **387** (1 gm, 1.14 mmol) were

coupled at room temperature. This reaction was repeated on the same scale as above for the resulting polymer to afford the MCM-41-Fmoc **390** as a white solid (1.135 g); υ_{max} (ATR) 1600 (C=O, amide), 1050, 1614, 844, 800, 438 cm^{-1}; δ_C VNMRS CP (100.562 MHz) 174 (C=O amide), 141 (Ar-C), 125 (Ar-C), 51 (*N*CH_2, $SiOCH_3$), 40 (Alk-C), 33 (*N*CH_3), 27 (CH_2), 10 ($SiCH_2$), 0.35 ($Si(CH_3)_3$).

6.2.33 Cleavage of Fmoc (369)



In a 25 ml microwave vessel, a mixture of polymer **390** (0.5 gm) and 20% of piperidine in dry DMF (15 ml) was shaken at r.t for 1 h. The resulting solid was washed by dry toluene, hexane and DCM, then dried *in vacuo* overnight at 60 ^oC to afford amine-MCM-41 **369** as a white solid (~0.50 gm); δ_C VNMRS CP (100.562 MHz) 174 (C=O amide), 141 (Ar-C), 125 (Ar-C), 51 (*N*CH_2, $SiOCH_3$), 40 (Alk-C), 33 (*N*CH_3), 27 (CH_2), 10 ($SiCH_2$), 0.35 ($Si(CH_3)_3$). The Beer-Lambert law was used to determine the concentration of the piperidine-fulvene adduct in both solutions described below in (**Table 45**) Lambert law:

$A = C \varepsilon l$

Entry No	**A (X)**	**mmol/g**	**A (Y)**	**mmol/g**	**Solution taken (ml)**
1	0.233	0.018	0.229	0.0177	0.15 ml to 3 ml
2	0.297	0.0172	0.297	0.0172	0.2 ml to 3 ml
3	0.372	0.0172	0.37	0.0171	0.25 ml to 3 ml
4	0.444	0.0171	0.443	0.0171	0.3 ml to 3 ml

Table 45: Determination of the loading on polymer using Lambert law

C = A/ Ɛ Ɛ = 7800, l = 1 cm at λ = 300

C = 0.233/7800 = 0.00002987 mol/dm = 0.02987 mmol/dm

Total mass before remove Fmoc = 500 mg/15 ml

The mass in 0.15 ml solution after remove Fmoc = 5 mg/3 ml = 1.66 g/dm

mmol/ g = (A/ Ɛ)/1.66 = 0,018

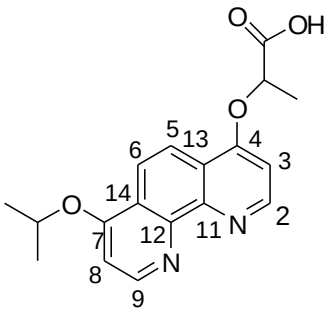
6.2.34 Hydrolysis of ester group

In a round bottomed flask, a mixture of ester (1.0 mmol) and $LiOH.H_2O$ (125 mg, 3.0 mmol) in 10 ml of (H_2O:MeOH 1:1) was stirred at room temprature for 18h.

Protocol W1: HCl solution was then added to acidify (pH = 4-5) and extracted into EtOAc (20 ml x 2). The aqueous layer was concentrated *in vacuo* to afford the title carboxylic acid compound without further purification.

Protocol W2: The reaction mixture was stirred overnight, solvent was then removed *in vacuo* to afford the 2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-lithium propanoate.

6.2.34.1 *2-(7-Isopropoxy-[1,10]-phenanthrolin-4-yloxy)-propionic acid* (395)



Following protocol **W1**, 2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-propionic acid ethyl ester **367** (354 mg) was hydrolysed by $LiOH.H_2O$ to afford without further purification, giving 2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-propionic acid **395** as an orange solid (0.1 g, 31%), (mp = > 150 ^oC decomp.); υ_{max} (ATR) 3391 (OH broad), 1614, 1587, 1538, 1479, 1411, 1295, 1284, 1241, 1209, 1188, 1091, 1048, 1015, 958, 847, 828, 731 626 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 8.7 (2H, d, *J* = 6.1 Hz, 2,9-*H*), 7.9 (1H, d, *J* = 9.2 Hz, 5-*H*), 7.8 (1H, d, *J* = 9.2 Hz, 6-*H*), 7.4 (1H, d, *J* = 6.1 Hz, 8-*H*), 7.1 (1H, d, *J* = 5.9 Hz, 3-*H*), 5.1 (1H, hept, *J* = 6.1 Hz, 7-OC*H*$(CH_3)_2$), 5.0 (1H, q, *J* = 6.7 Hz, 4-OC*H*(CH_3)), 1.8 (3H, d, *J* = 6.7 Hz, 4-OCH(C*H*$_3$)), 1.6-1.5 (6H, m, 7-OCH(C*H*$_3)_2$)); δ_C (151 MHz, $CDCl_3$) 176.5 (*C*=*O*), 165.1 (*C*-7), 164.9 (*C*-4), 150.1 (Ar-*C*), 149.4 (Ar-*C*), 140.0 (*C*-11), 139.7 (*C*-12), 122.1 (*C*-14), 122.0 (*C*-13), 120.9 (*C*-5), 120.1 (*C*-6), 107.2 (*C*-3), 107.0 (*C*-8), 77.8 (4-O*C*H(CH_3)), 75.2 (7-O*C*H$(CH_3)_2$), 22,0 (Ala-*C*), 21.9 (Ala-*C*), 19.1 (4-OCH(*C*H$_3$)); *m/z* (LC-MS, EI^-) 651 ($[M_2\text{-}H]^-$, 100%), 325 ($[M\text{-}H]^-$, 48%); HRMS (ES^+) found ($[MH]^+$) 327.1355; $C_{18}H_{19}N_2O_4$ requires M, 327.1345.

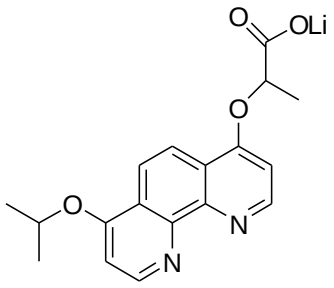
6.2.35 The coupling of lithium carboxylic salt with amine

Under N_2, in a round bottomed flask, 2-(7-Isopropoxy-[1,10]-phenanthrolin-4-yloxy)-lithium propanoate (X mmol) was added to the amine (X mmol) in dry DMF (X ml) at 0 ^oC, HBTU (X mmol) was then added and the mixture was stirred at r.t ^oC for 24 h. The reaction mixture was worked up and purification achieved by the stated method.

Protocol X1: DMF solvent was removed *in vacuo* then re-dissolved in DCM, washed (aq. $NaHCO_3$), dried over $MgSO_4$ and concentrated *in vacuo* to afford, following chromatography (C-18 SiO_2), the title amide compound.

Protocol X2: The reaction mixture was filtered *in vacuo* and then washed with dry DMF, DCM and MeOH. The resulting solid was dried *in vacuo* at 65 ^oC overnight to afford the title amid compound.

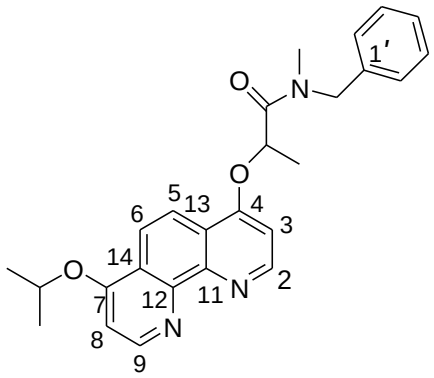
6.2.35.1 *2-(7-Isopropoxy-[1,10]-phenanthrolin-4-yloxy)-propionic acid lithium salt* (368)



Following protocol **W2**, 2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-propionic acid ethyl ester **367** (354 mg) hydrolysed by LiOH . H_2O to afford the 2-(7-isopropoxy-[1,10]-

phenanthrolin-4-yloxy)-lithium propanoate **368** (0.52 g), which was used directly in the next step with no purification required.

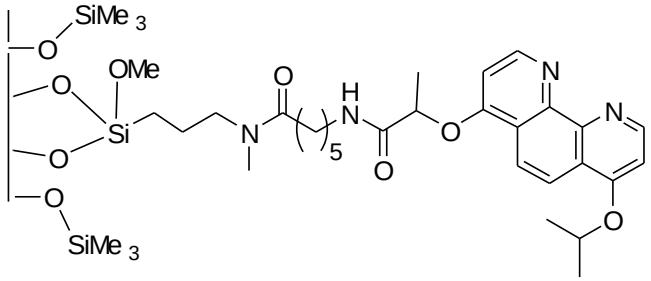
6.2.35.2 ***N-Benzyl-2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-N-methyl-propionamide*** **(396)**



Following protocol **X1**, 2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-lithium propanoate **368** (0.275 mmol, 91.3 mg), *N*-benzylmethylamine **392** (0.25 mmol, 33 µl) in DMF (2 ml) and HBTU (0.275 mmol, 104.3 mg) were coupled at r.t ^{o}C to afford the *N*-benzyl-2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-*N*-methyl-propionamide **396** as an orange solid (25 mg, 23%). (mp = undetected); υ_{max} (ATR) 1652 (C=O, amide), 1585, 1568, 1511, 1498, 1421, 1308, 1283, 1229, 1082, 1008, 955, 823, 733, 698 $cm^{-1}\delta_H$; (700 MHz, $CDCl_3$) 9.0 (1H, d, *J* = 5.2 Hz, 9-*H*), 8.95 (0.7H, d, *J* = 5.2 Hz, 2-*H*, rotamer A), 8.9 (0.3H, d, *J* = 5.2 Hz, 2-*H*, rotamer B), 8.23-8.15 (1.4H, m, 5, 6-*H*, rotamer A), 8.13-8.1 (0.6H, m, 5, 6-*H*, rotamer B), 7.30-7.20 (3H, m, Ar-*H*), 7.2-7.13 (1.6H, m, Ar-*H*, rotamer A), 7.1 (0.6H d, *J* = 7.5 Hz, Ar-*H*, rotamer B), 7.0 (1H, d, *J* = 5.2 Hz, 8-*H*), 6.9 (0.7H, d, *J* = 5.2 Hz, 3-*H*, rotamer A), 6.8 (0.3H, d, *J* = 5.2 Hz, 3-*H*, rotamer B), 5.36-5.3 (1H, m, 4-O-C*H*, rotamers A and B), 4.91-4.85 (1H, m, 7-OC*H*(CH_3), rotamers A and B), 4.78-4.65 (0.5H, m, Ar-CH_2, rotamer A), 4.65-4.53 (1.5H, m, Ar-CH_2, rotamer B), 3.0 (2H, s, *NCH*$_3$,

rotamer B), 2.9 (1H, s, *NCH*$_3$, rotamer A), 1.9 (2H, d, *J* = 6.7 Hz, 15-C*H*$_3$, rotamer B), 1.8 (1H, d, *J* = 6.7 Hz, 15-C*H*$_3$, rotamer A), 1.5 (6H, m, 7-OCH(C*H*$_3$)$_2$, rotamer A and B); δ_C (176 MHz, $CDCl_3$) 170.4 (*C*=O, rotamer A), 170.0 (*C*=O, rotamer B), 161.1 (*C*-7), 160.3 (*C*-4, rotamer B), 160.2 (*C*-4, rotamer A), 151.0 (*C*-9), 150.9 (*C*-2, rotamer A and B), 146.8 (*C*-11), 146.6 (*C*-12), 136.6 (*C*-1', rotamer B), 135.9 (*C*-1', rotamer A), 129.0 (Ar-*C*), 128.8 (Ar-*C*), 128.1 (Ar-*C*), 127.9 (Ar-*C*), 127.8 (Ar-*C*), 126.5 (Ar-*C*), 121.8 (*C*-14, rotamer A), 121.7 (*C*-14, rotamer B), 120.1 (*C*-13, rotamer B), 120.0 (*C*-13, rotamer A), 119.8 (Ar-*C*, rotamer A), 119.7 (Ar-*C*, rotamer B), 118.8 (Ar-*C*, rotamer B), 118.7 (Ar-*C*, rotamer A), 104.3 (*C*-8), 104.2 (*C*-3, rotamers A and B), 74.5 (4-O-*C*H, rotamer A), 74.1 (4-O-*C*H, rotamer B), 71.4 (7-O-*C*H), 52.8 (Ar-*C*H$_2$, rotamer A), 51.9 (Ar-*C*H$_2$, rotamer B), 34.9 (*NC*H$_3$, rotamer A), 34.3 (*NC*H$_3$, rotamer B), 21.94 (7-O-CH(*C*H$_3$)$_2$, rotamers A and B), 18.6 (4-O*C*H(CH$_3$), rotamer A), 17.6 (4-OCH(*C*H$_3$), rotamer B); *m/z* (ASAP) 881 ([M$_2$H]$^+$, 15%), 430 ([MH]$^+$, 100%), 749 ([M$_2$Na]$^+$, 20%); HRMS (ASAP) found ([MH]$^+$) 430.2131; $C_{26}H_{28}N_3O_3$ requires M, 430.2131.

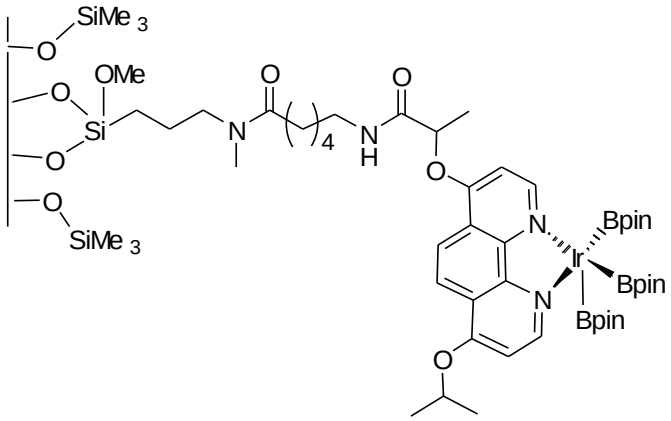
6.2.35.3 *Coupling of amine-MCM-41 with carboxylic lithium salt* (391)



Following protocol **X2**, a mixture of 2-(7-isopropoxy-[1,10]-phenanthrolin-4-yloxy)-lithium propanoate **368** (18.4 mg, 55.5 μmol), amine-MCM-41 **369** (1 gm, 0.018 mmol)

in dry DMF (10 ml) and HBTU (21 mg, 55.5 µmol) was coupled at r.t ^{o}C to afford the (MCM-41) **391** as a white solid which was then used as ligand in the next section.

6.2.36 *Preparation of silica supported iridium catalyst* (397)



A mixture of $[Ir(OMe)(cod)]_2$ (3.6 mg, 0.0054 mmol), silica supported ligand **391** (0.3 gm, 0.0054 mmol) and B_2pin_2 (4.1 mg, 0.0162 mmol) was placed in the reaction vessel (a filter tube) which was then sealed, evacuated and backfilled with N_2. THF (2 ml) was then added and the reaction mixture was heated at 50 ^{o}C for 10 min before washing with dry THF (3 x 10 ml). The resulting product was dried *in vacuo*, which was used directly in the borylation reaction in next section.

6.2.37 Borylation of m-xylene

Under N_2, m-xylene was added to the filter tube containing silica supported iridium **397** in THF (2 ml). The reaction mixture was heated at 80 ^{o}C for 6 h before washing with dry THF (3 x 10 ml). The resulting product solution was then concentrated *in vacuo*.

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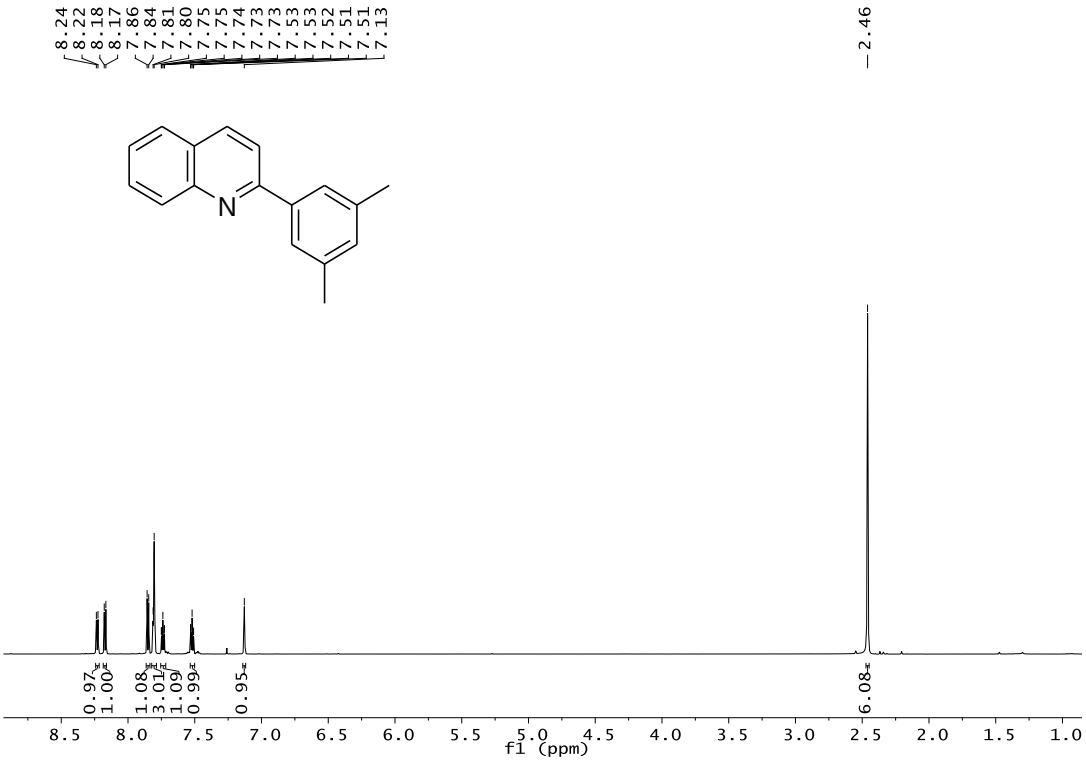
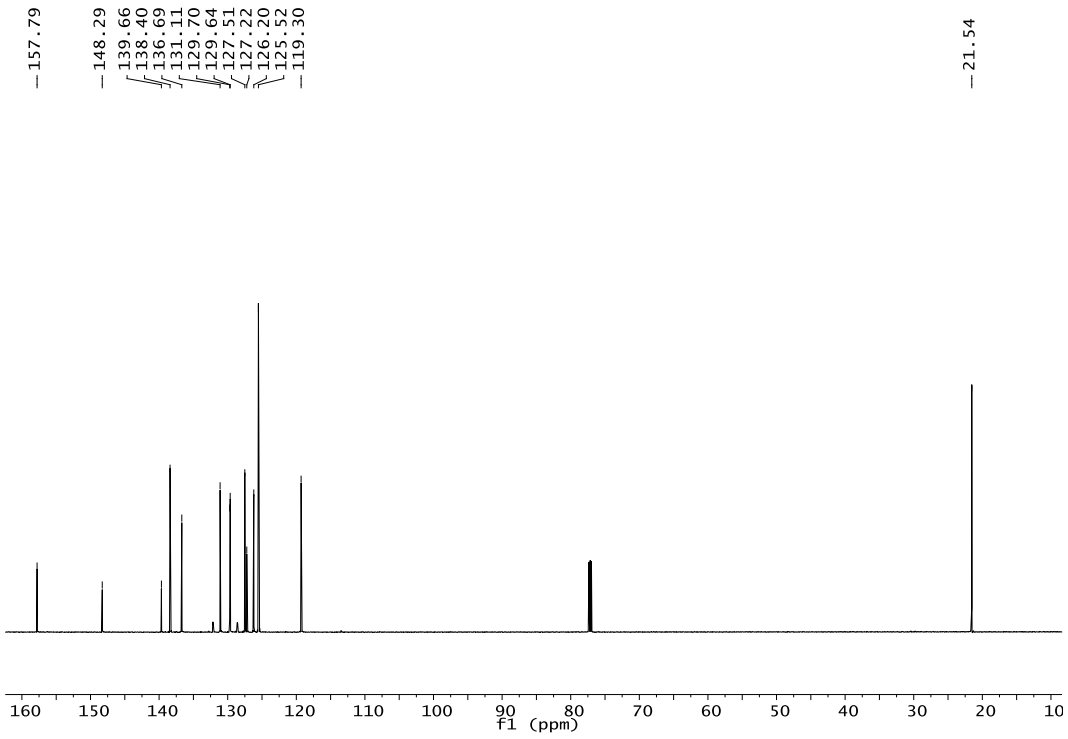
8 Appendix

^{1}H NMR (700 MHz, $CDCl_3$) - 199



^{13}C NMR (176 MHz, $CDCl_3$) - 199



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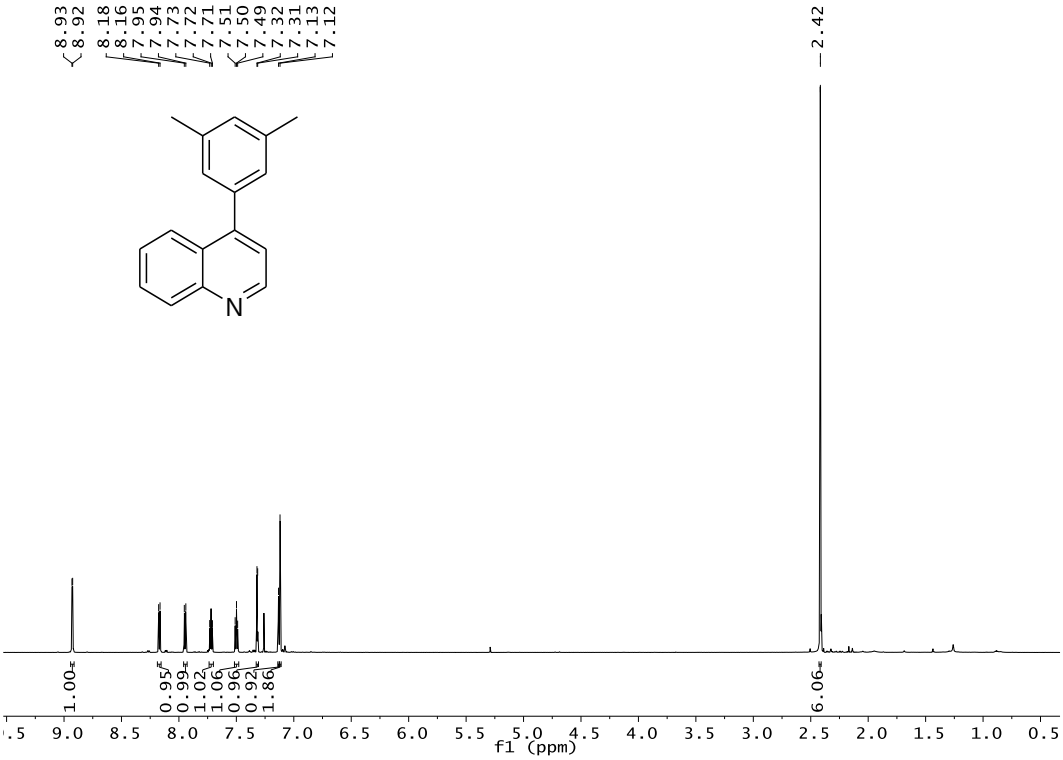

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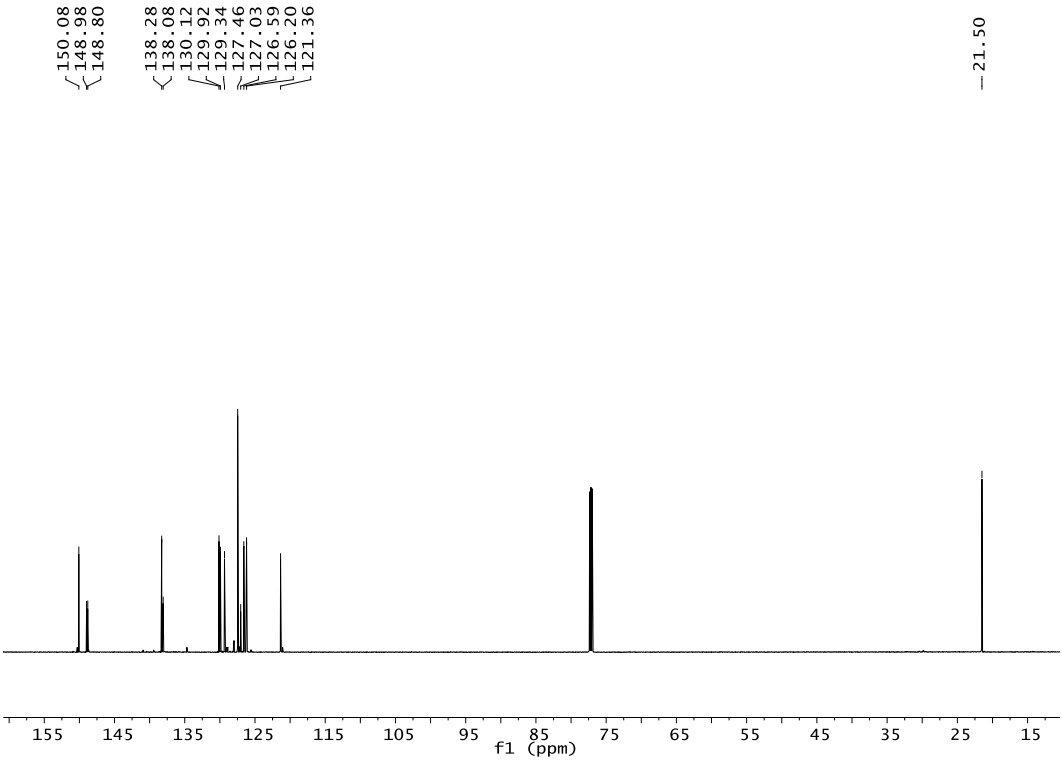
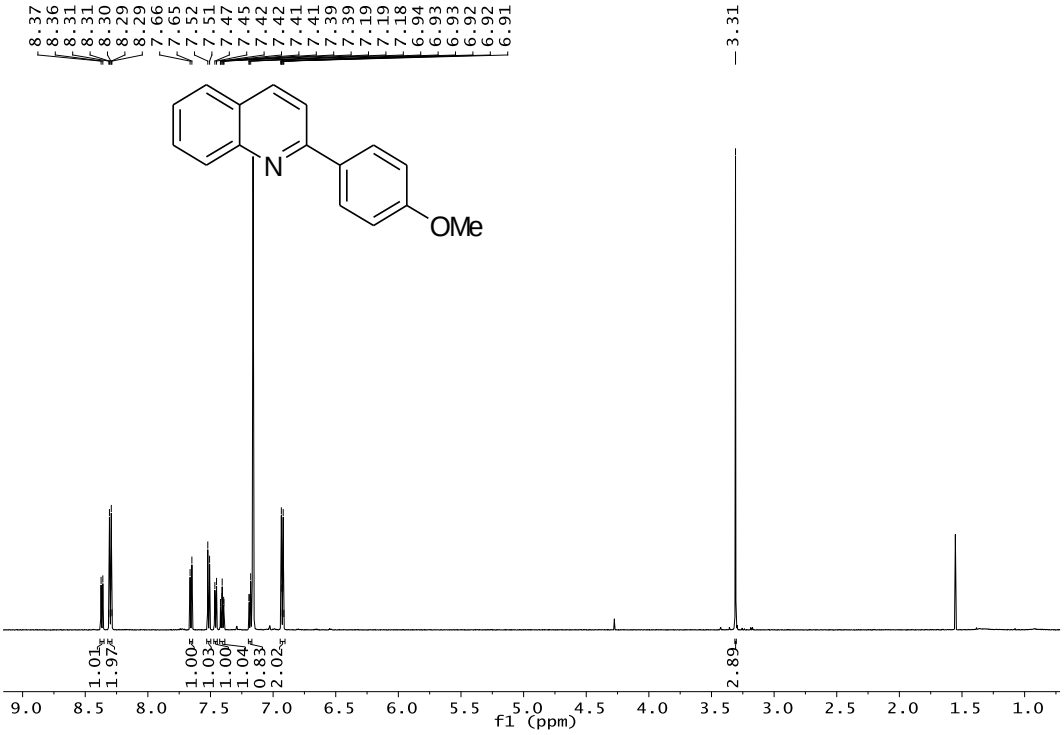


^{1}H NMR (600 MHz, C_6D_6) - 205



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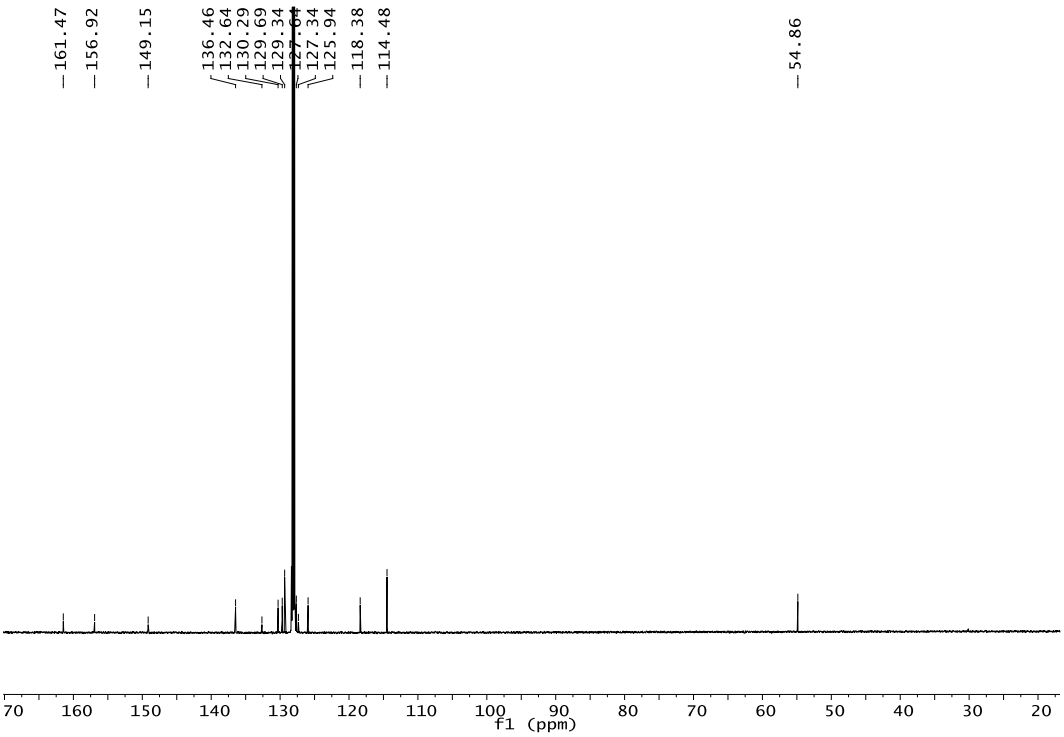
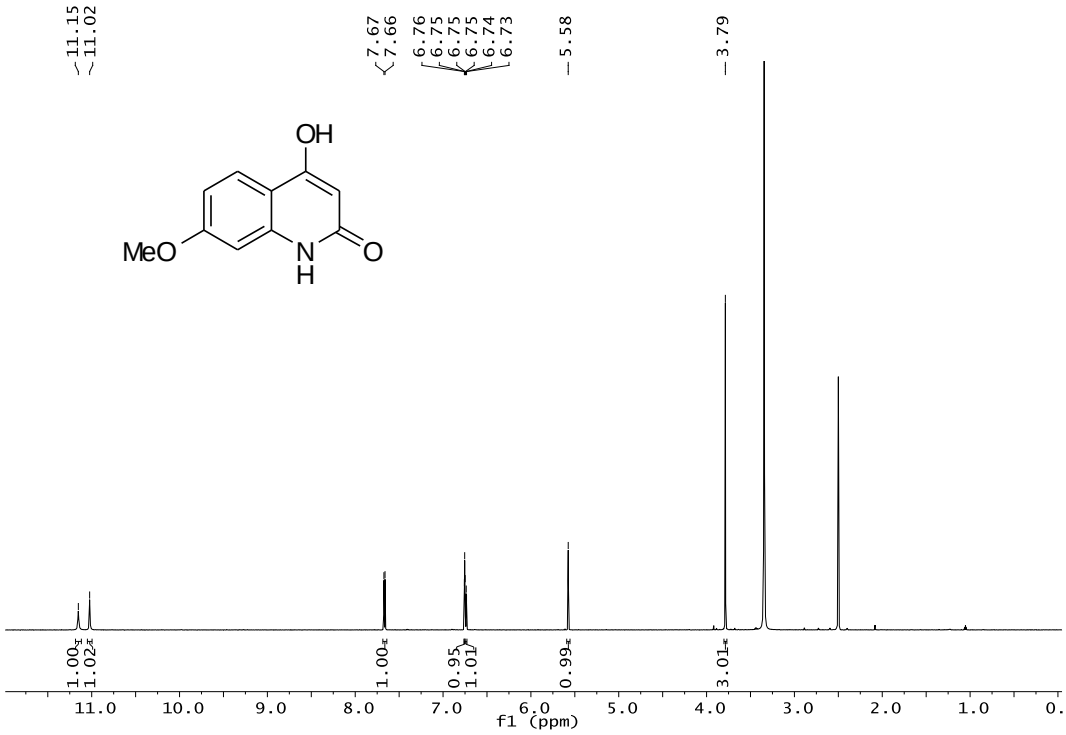


^{1}H NMR (700 MHz, d_6-DMSO) - 211



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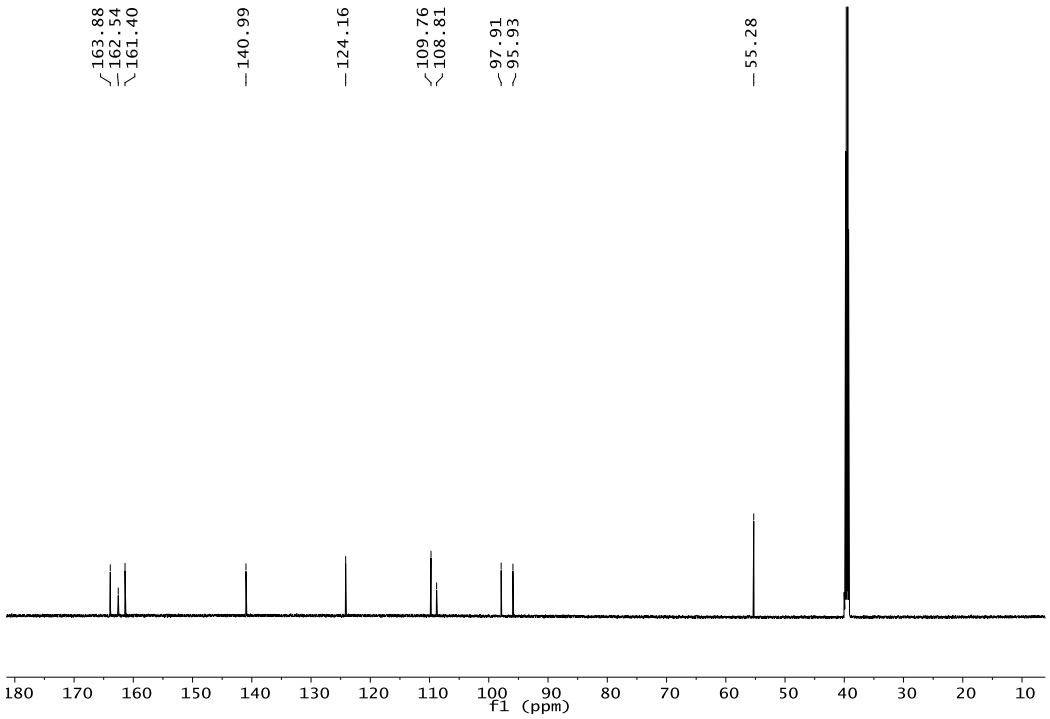

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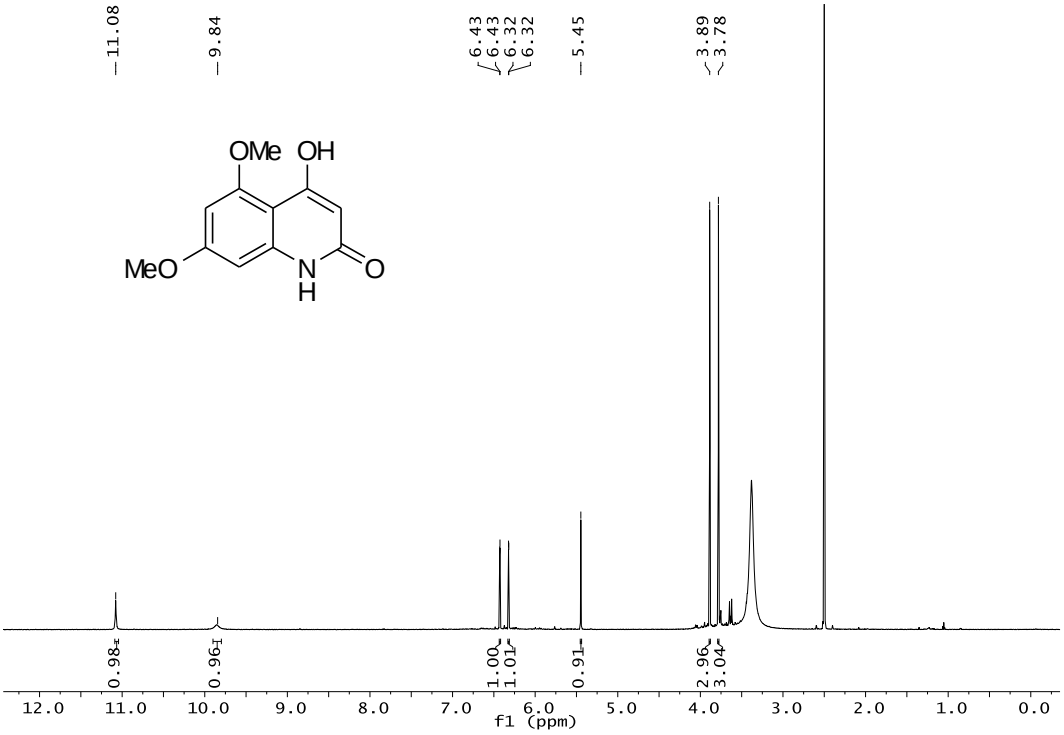

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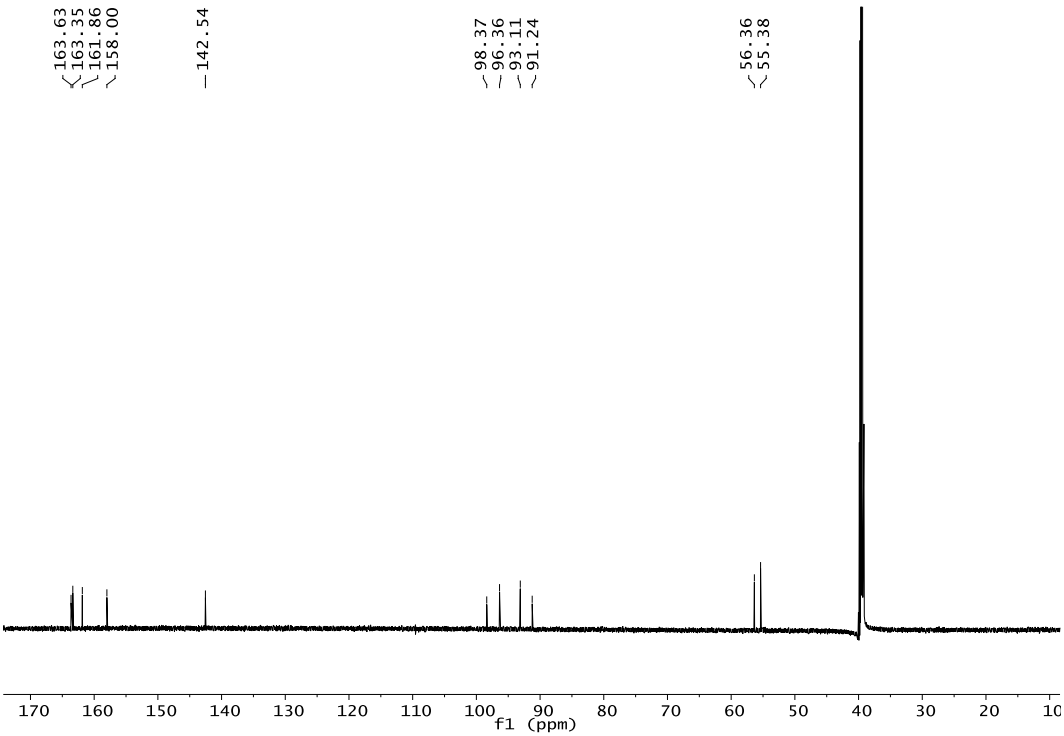
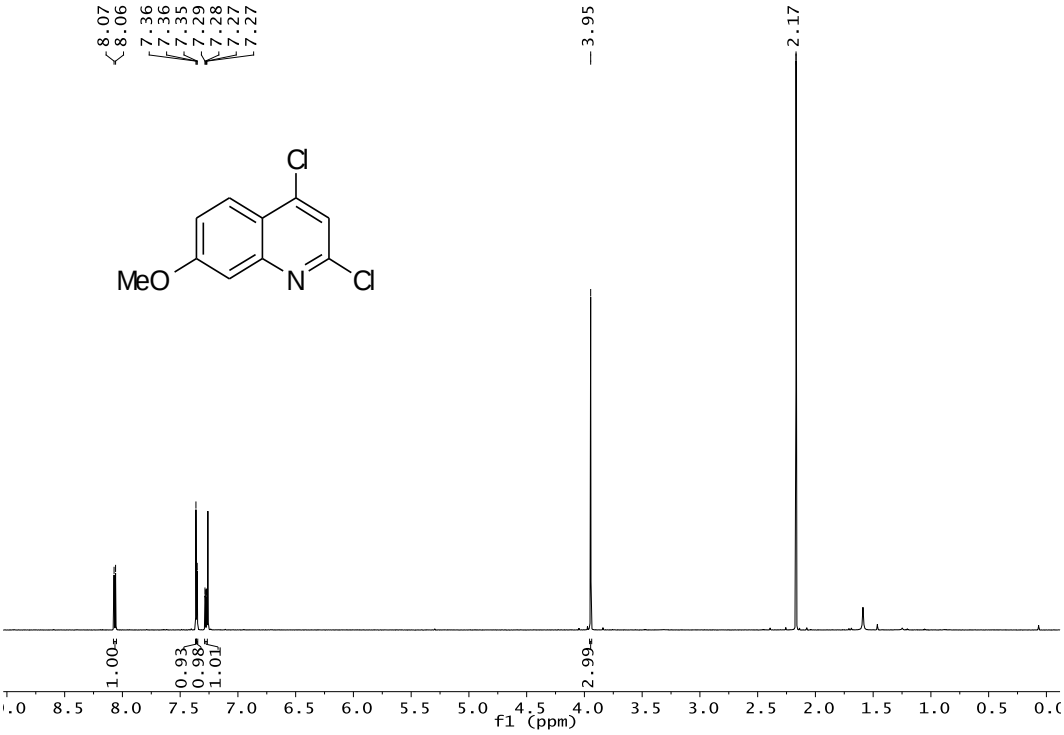


^{1}H NMR (700 MHz, $CDCl_3$) - 213



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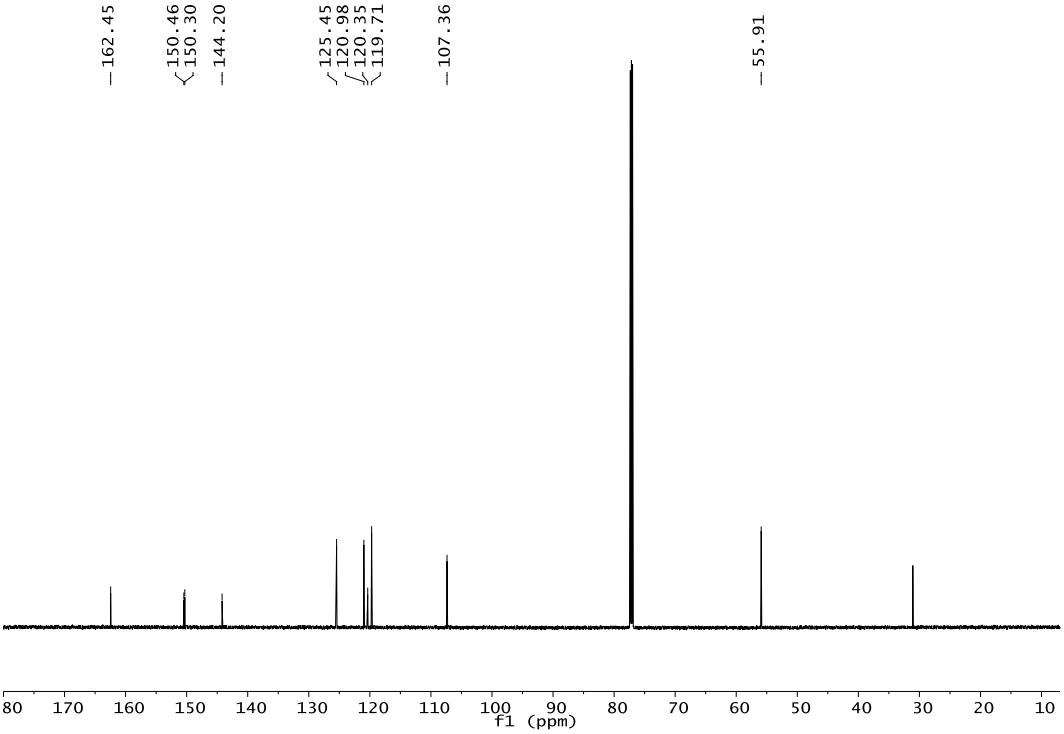

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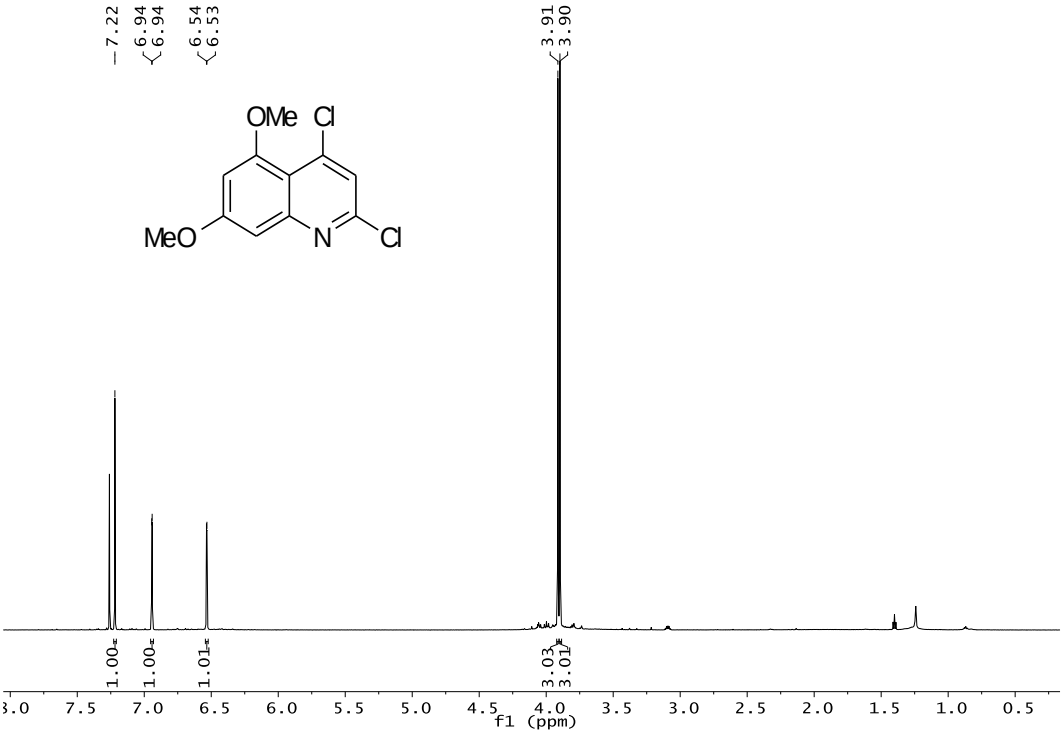

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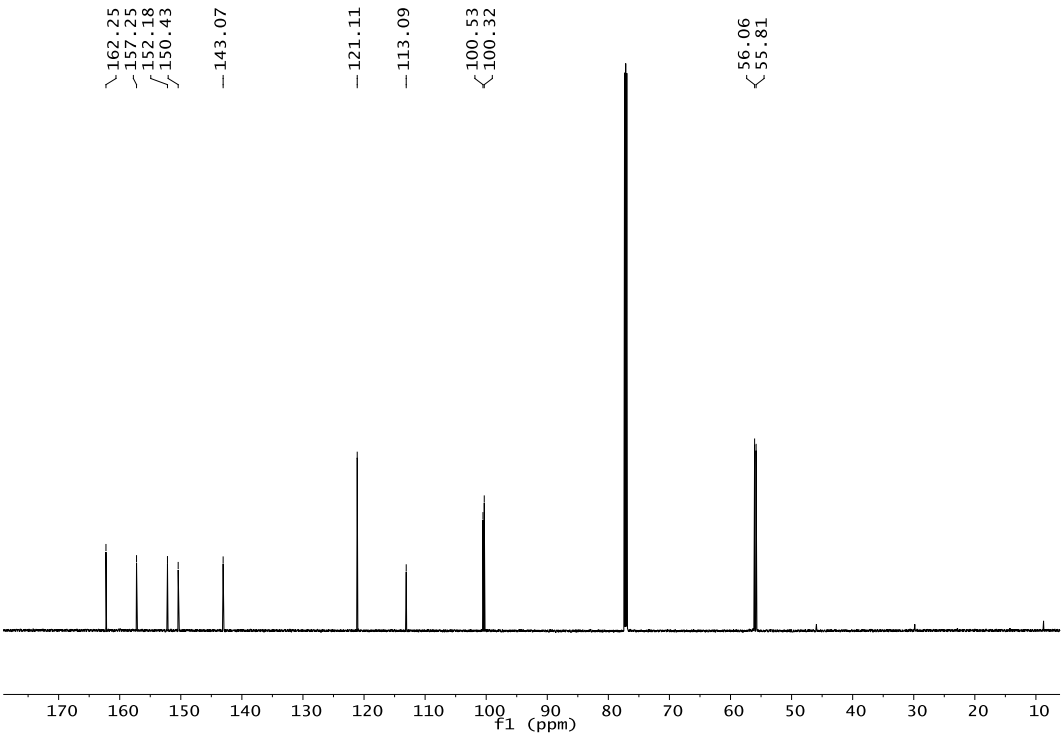

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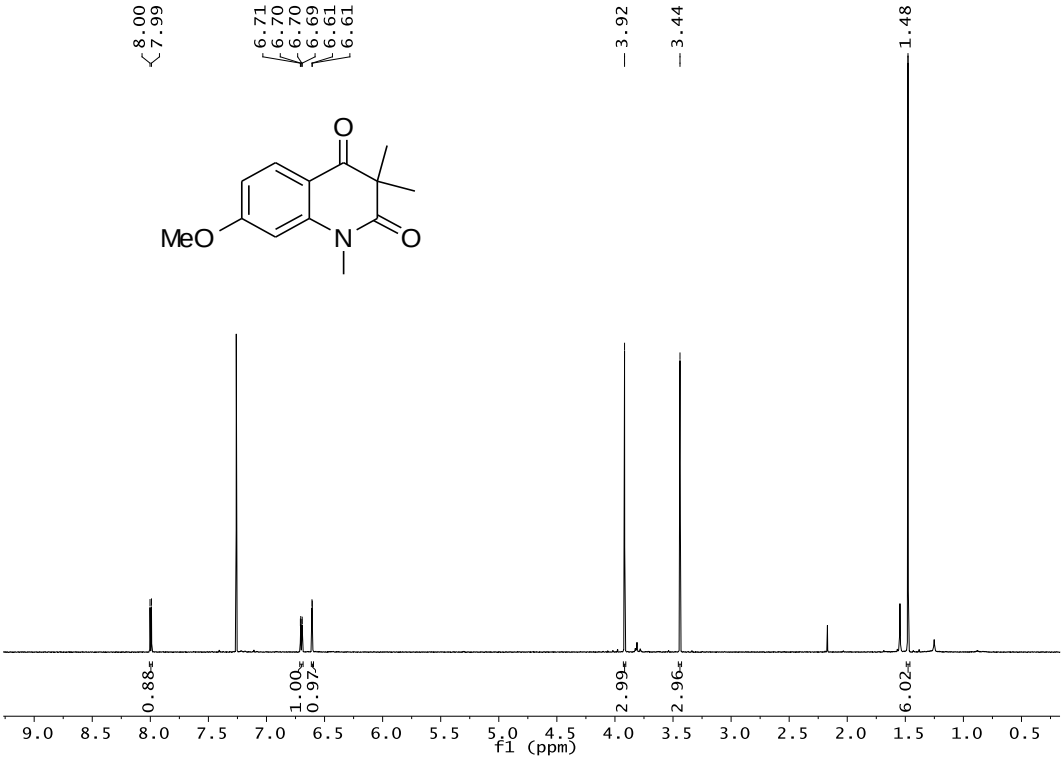

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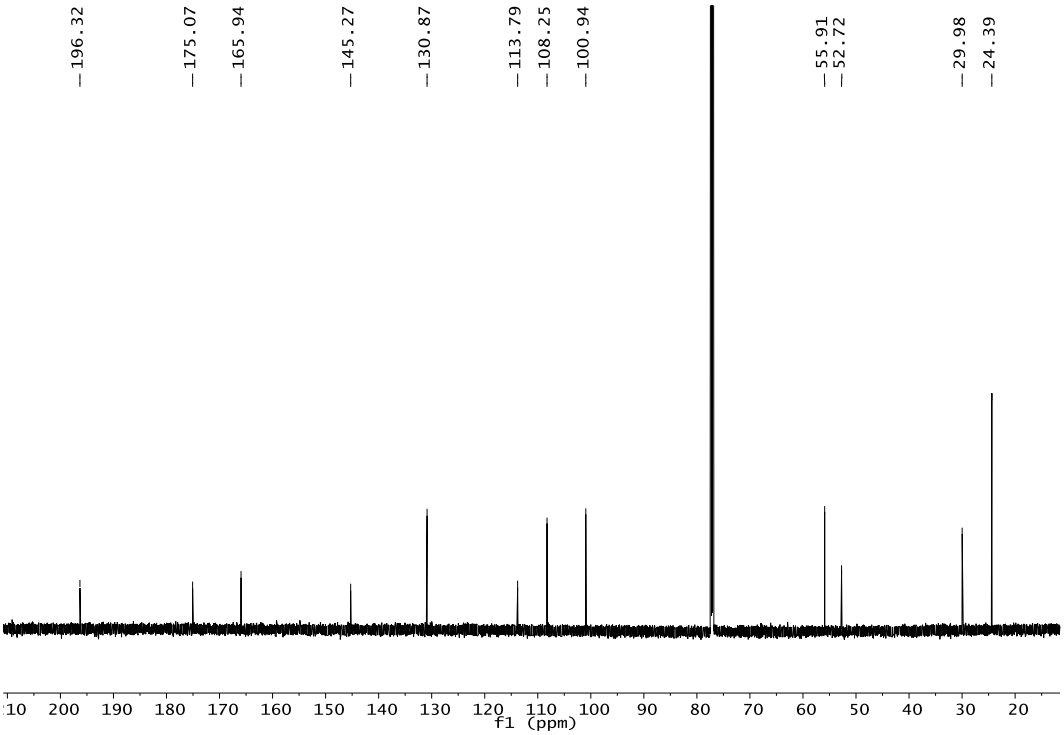

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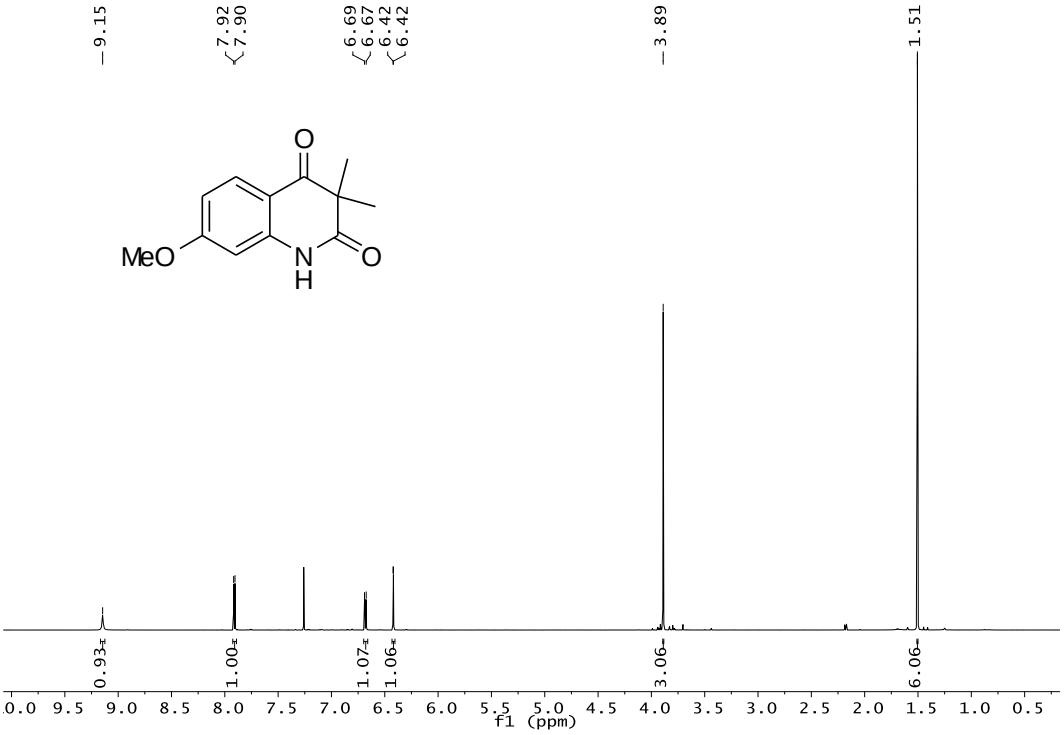

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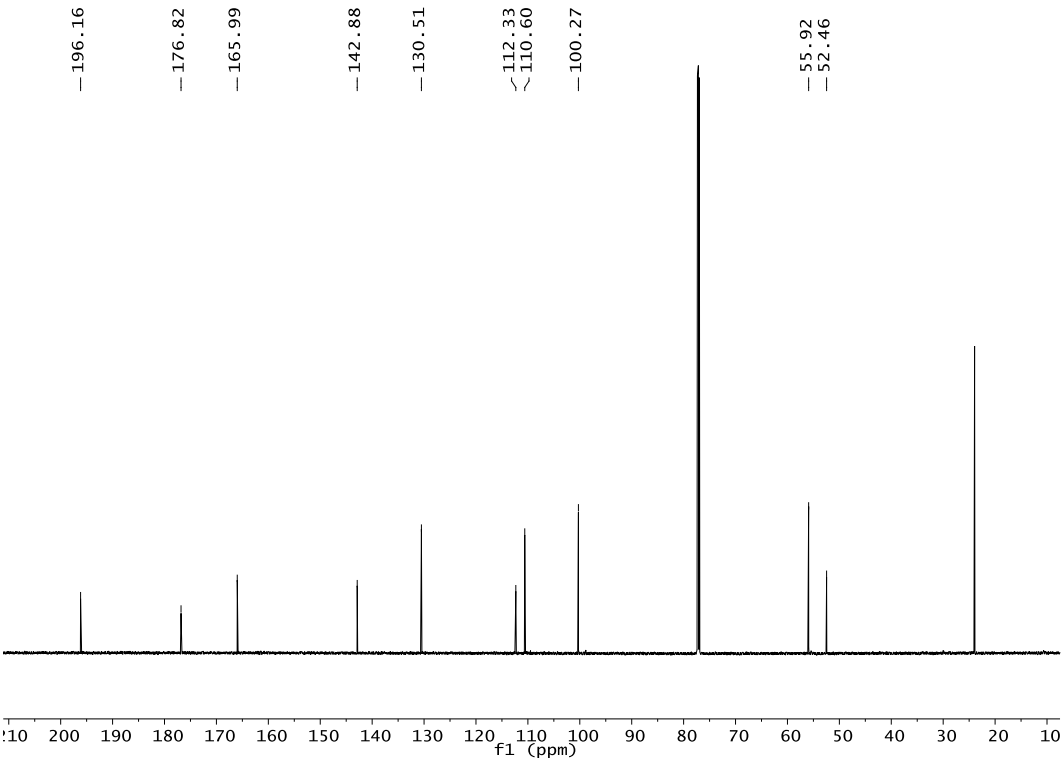

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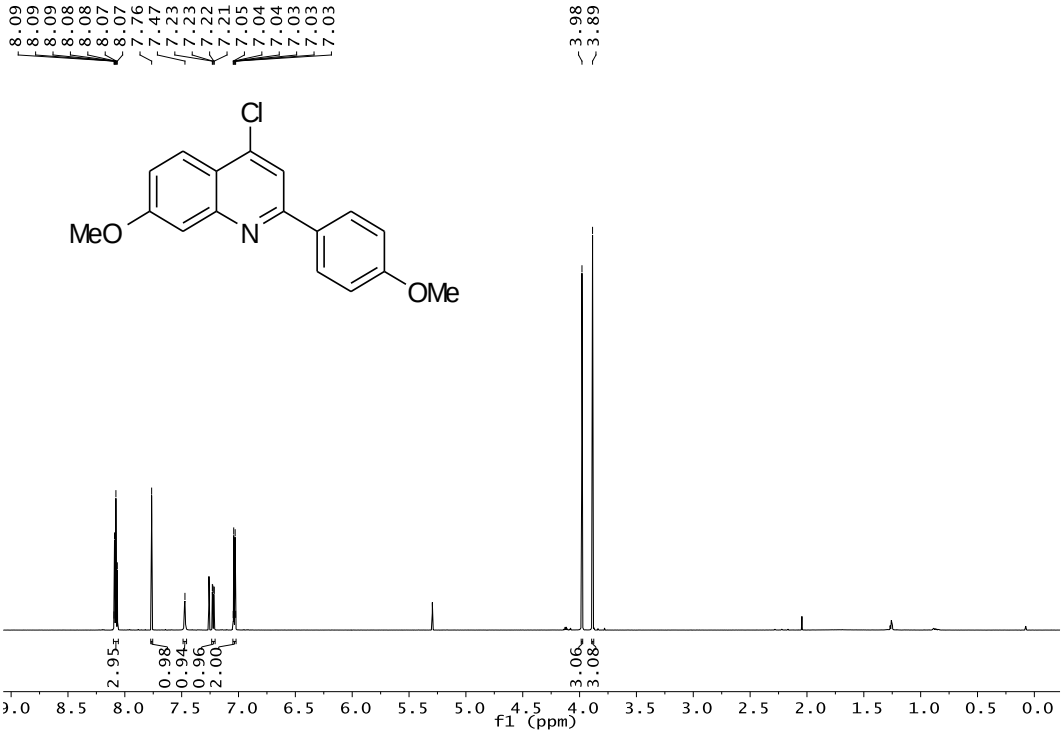
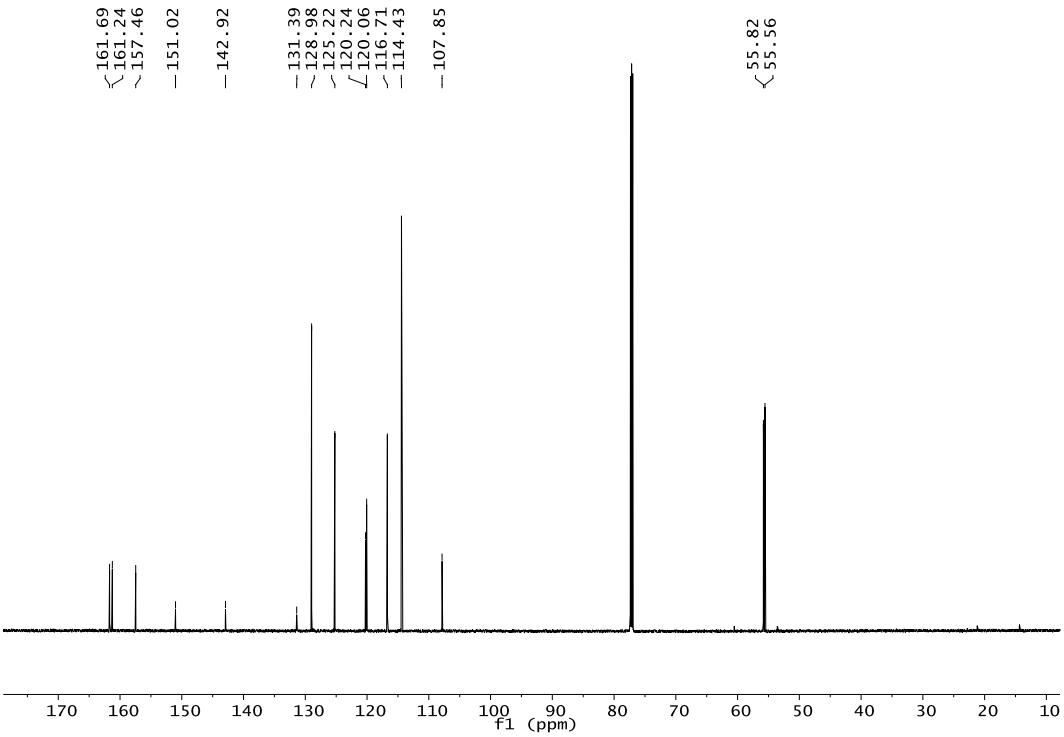
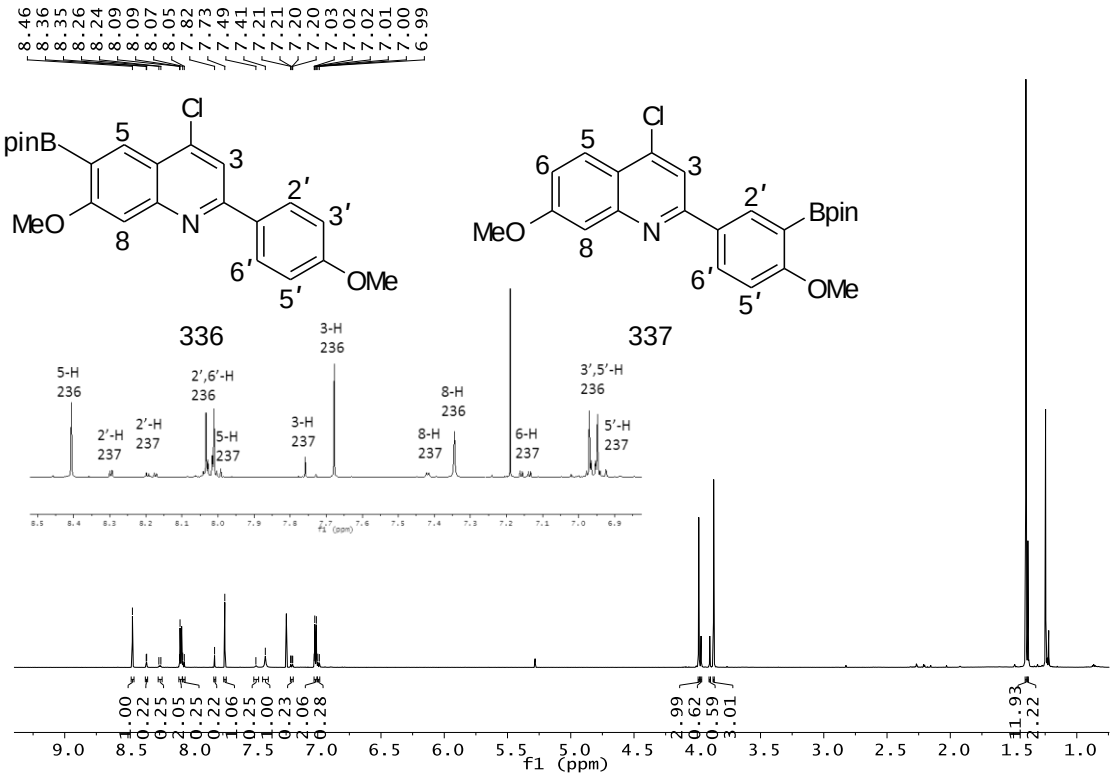


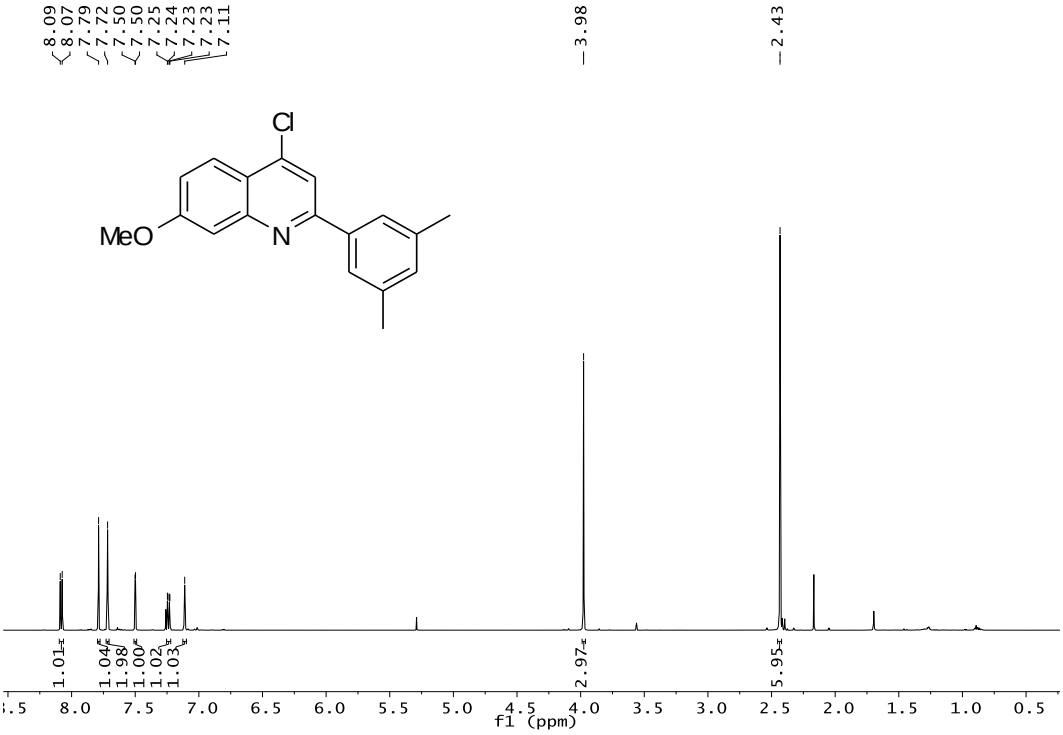
^{13}C NMR (176 MHz, $CDCl_3$) - 230



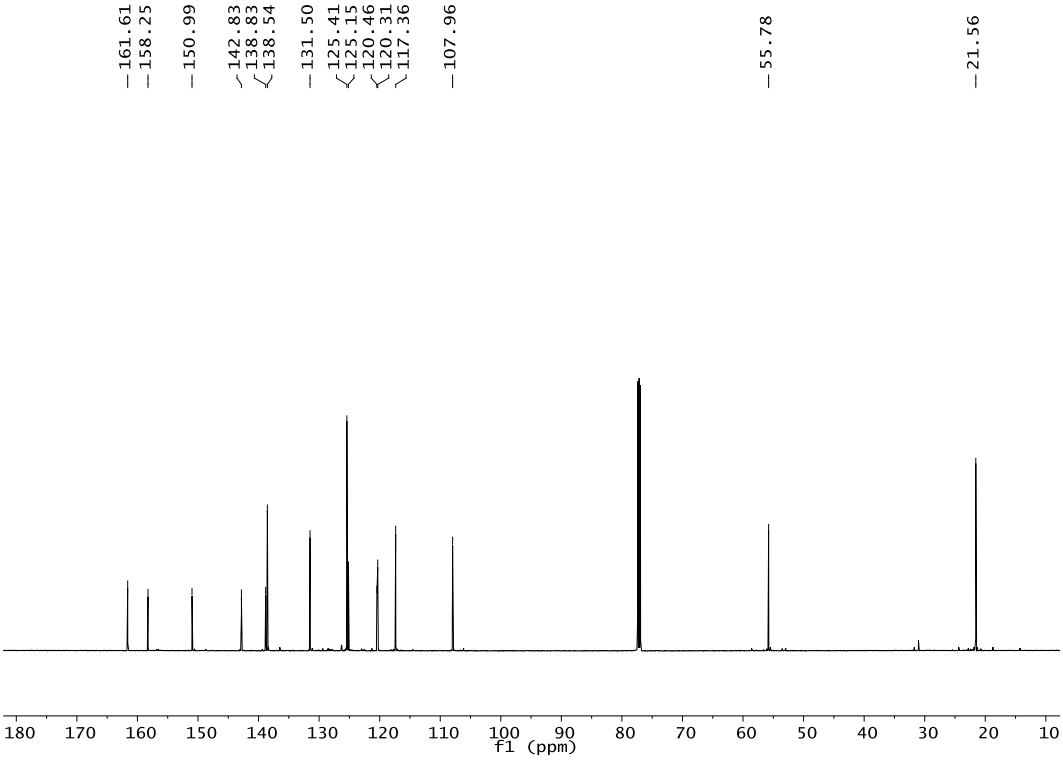
^{1}H NMR (700 MHz, $CDCl_3$) – Borylation of 230



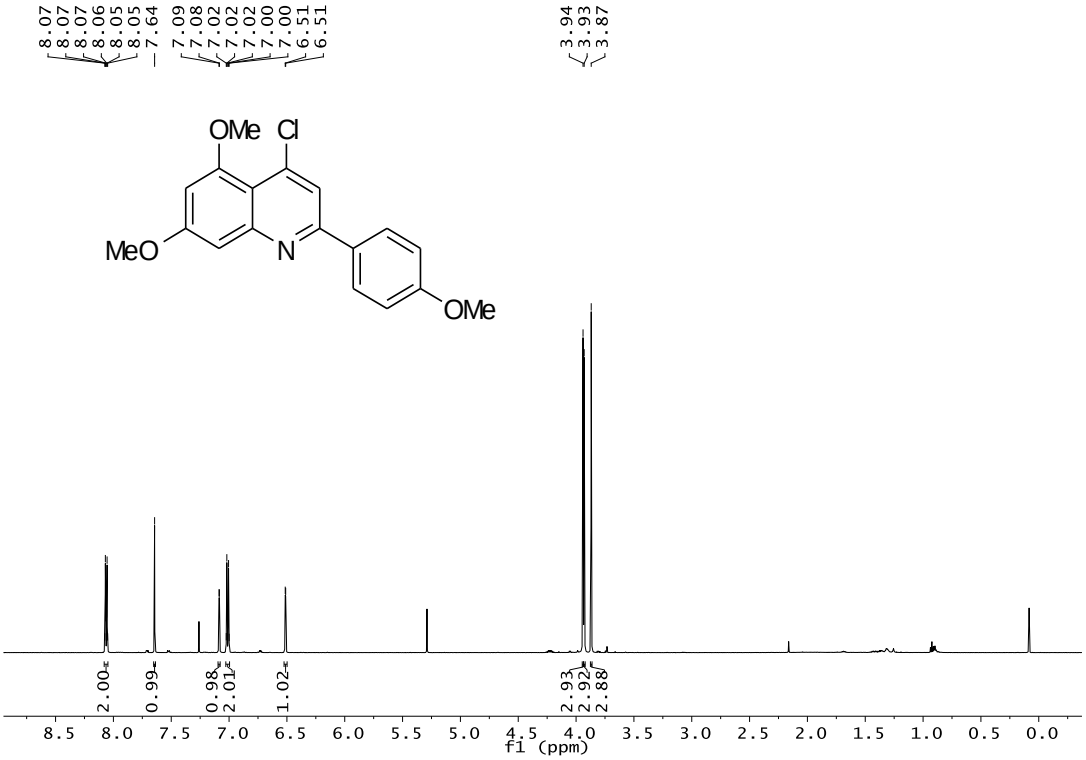
^{1}H NMR (600 MHz, $CDCl_3$) - 233



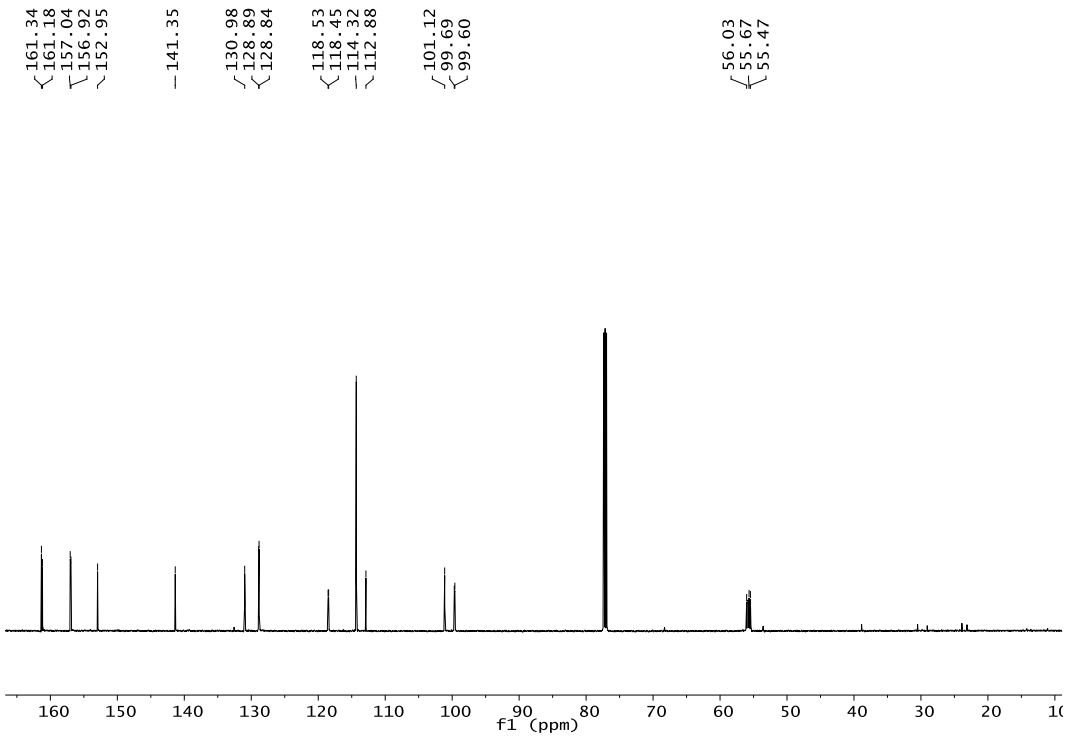
^{13}C NMR (151 MHz, $CDCl_3$) - 233



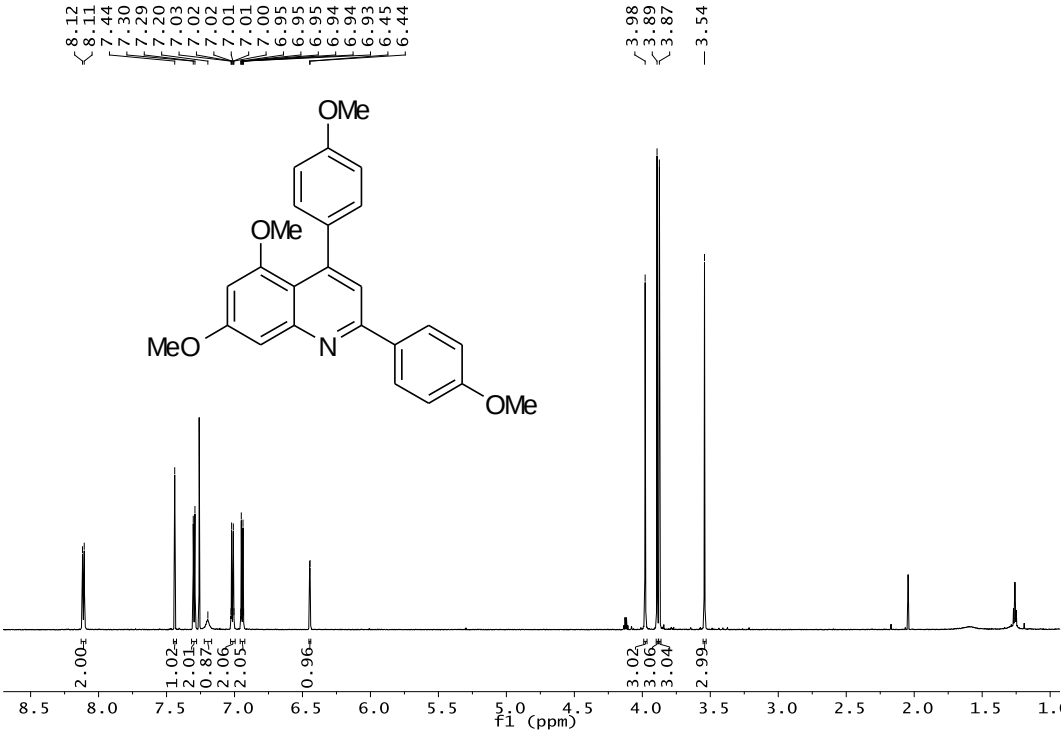
^{1}H NMR (700 MHz, $CDCl_3$) - 234



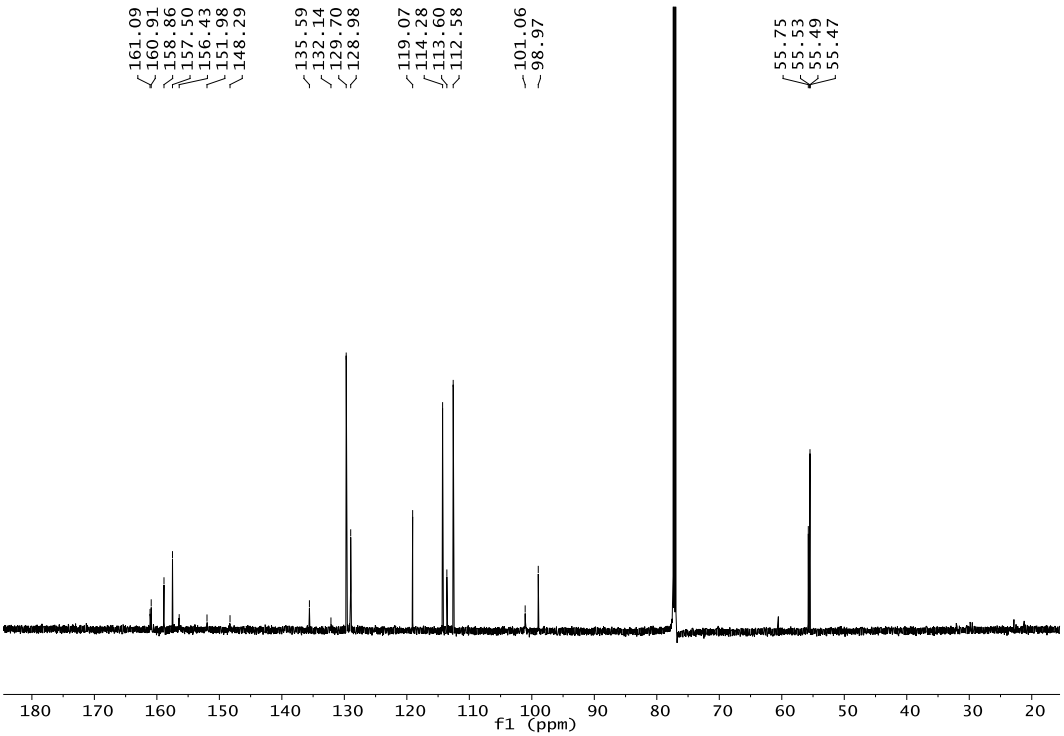
^{13}C NMR (176 MHz, $CDCl_3$) - 234



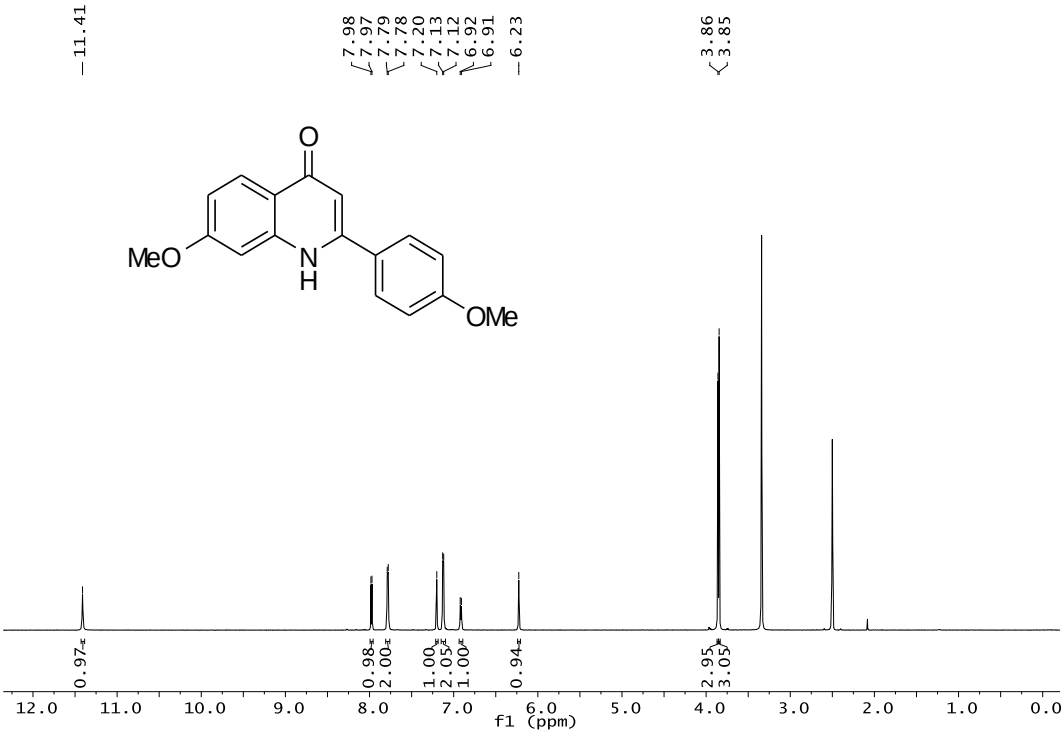
^{1}H NMR (700 MHz, $CDCl_3$) - 235



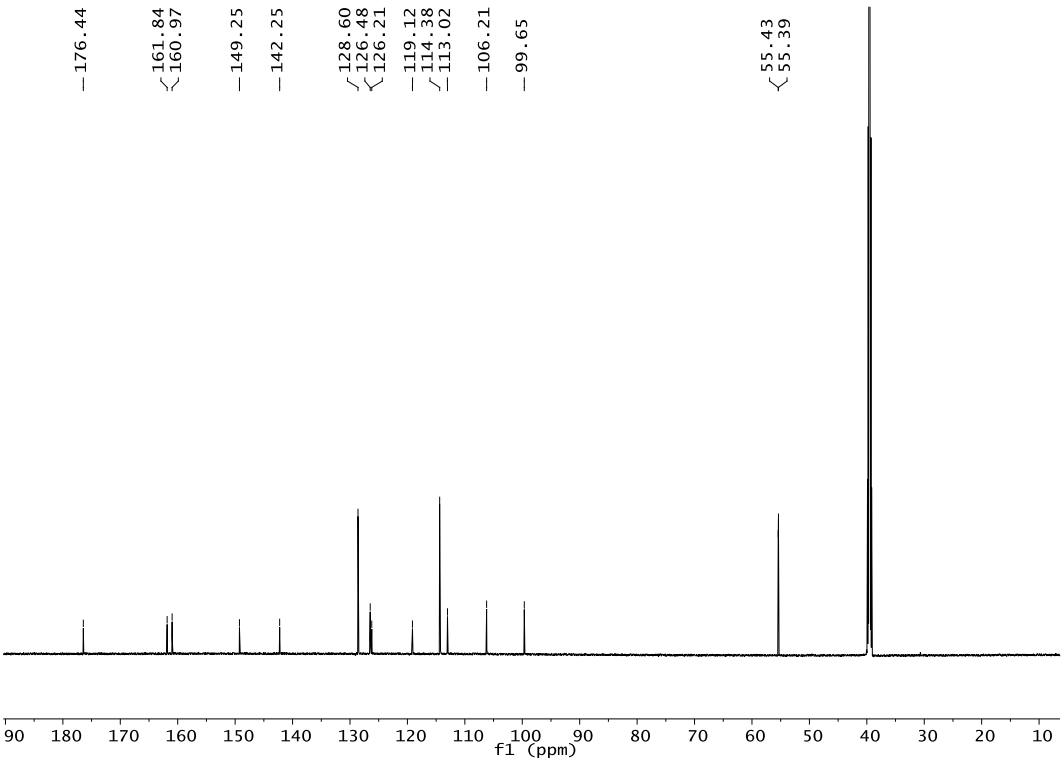
^{13}C NMR (176 MHz, $CDCl_3$) - 235



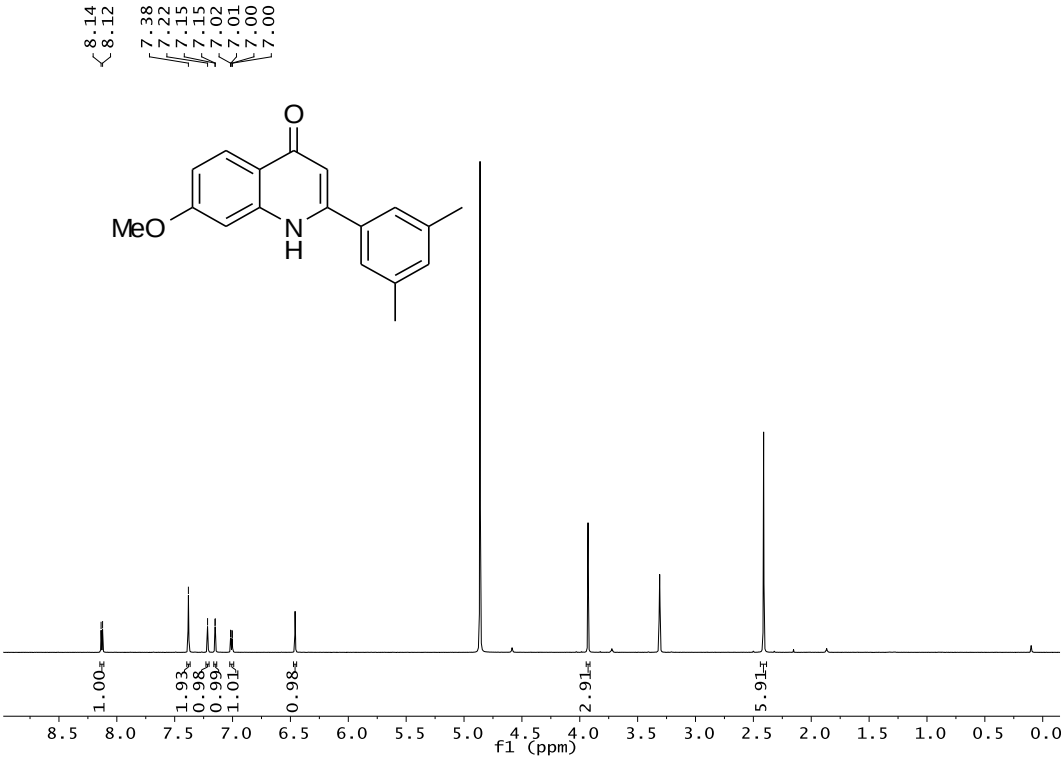
^{1}H NMR (700 MHz, d_6-DMSO) - 192B



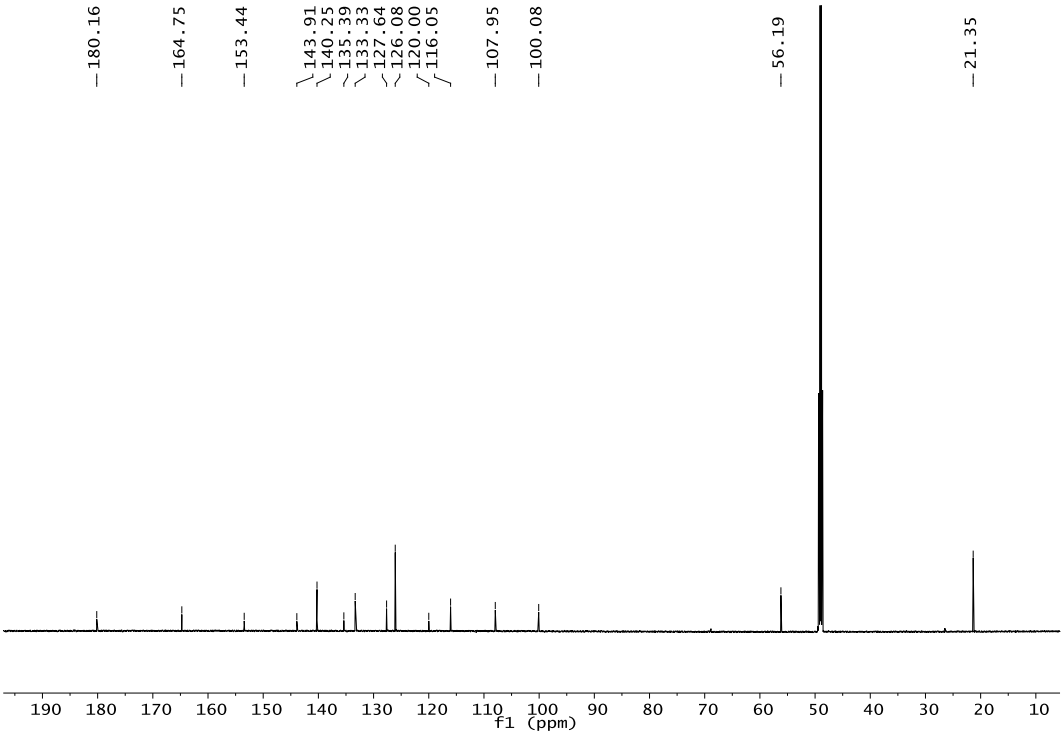
^{13}C NMR (176 MHz, d_6-DMSO) - 192B



^{1}H NMR (700 MHz, d_4-Methanol) - 240B

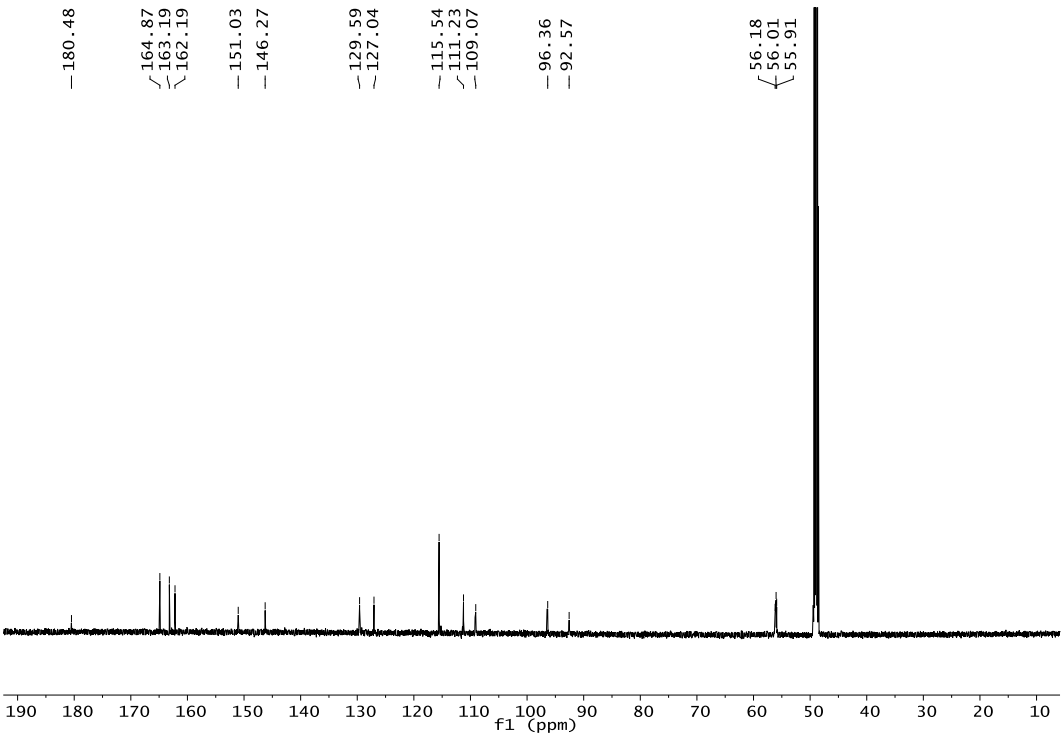


^{13}C NMR (176 MHz, d_4-Methanol) - 240B

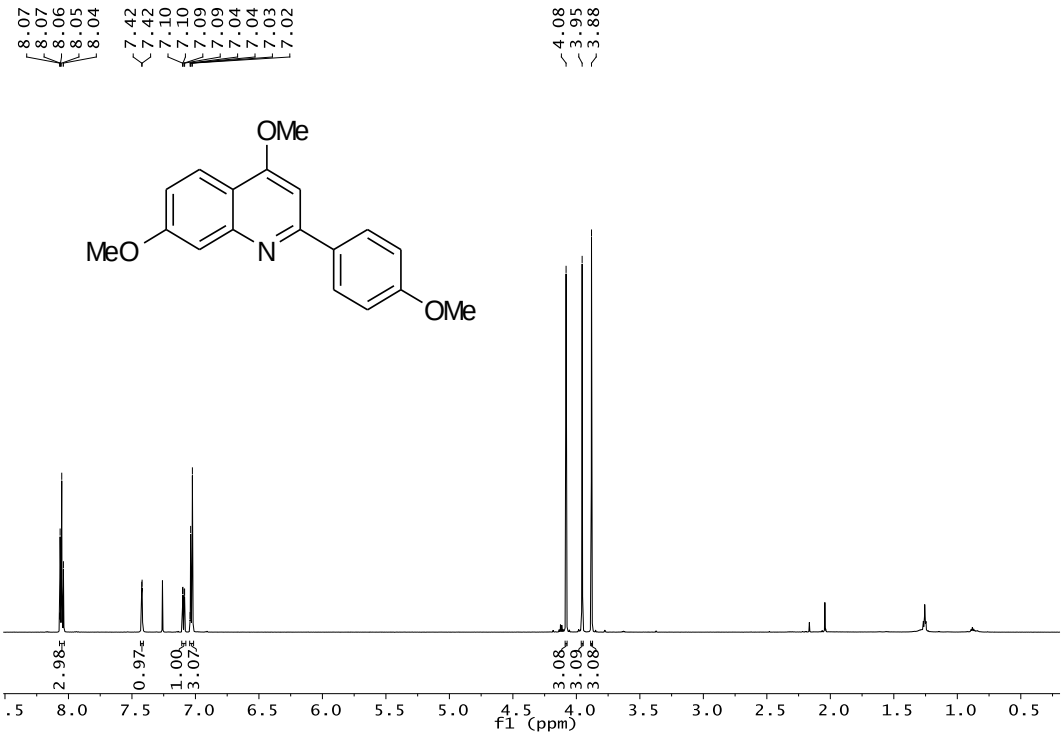


^{1}H NMR (600 MHz, Methanol-d_4) - 241A

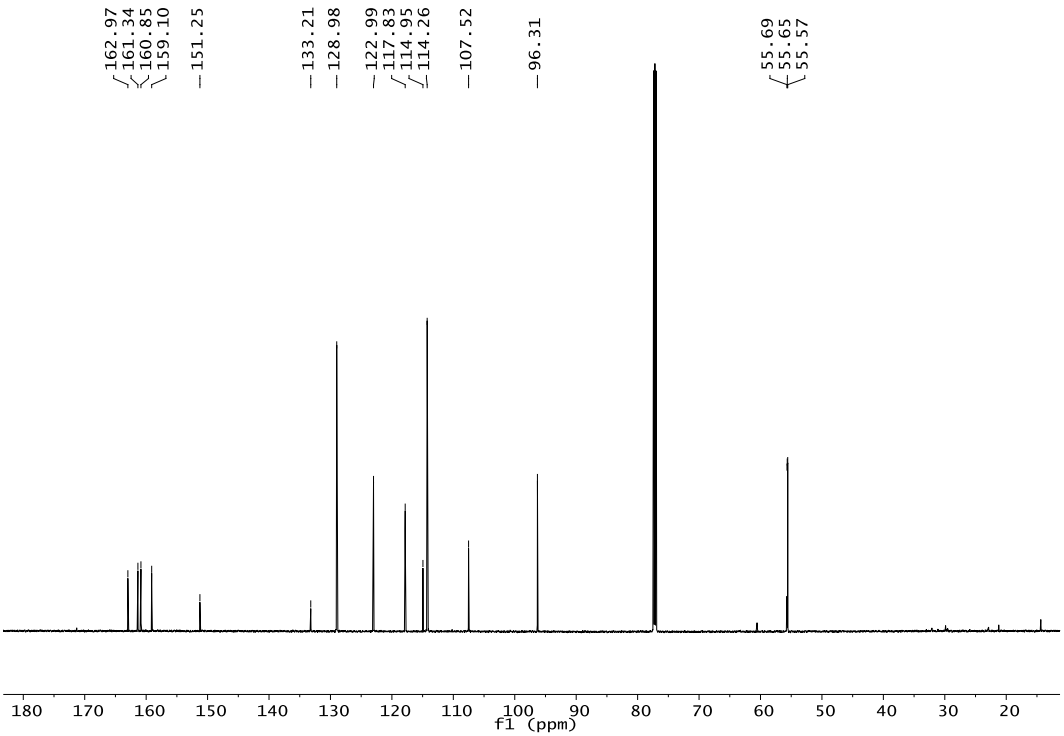
^{13}C NMR (151 MHz, Methanol-d_4) - 241A



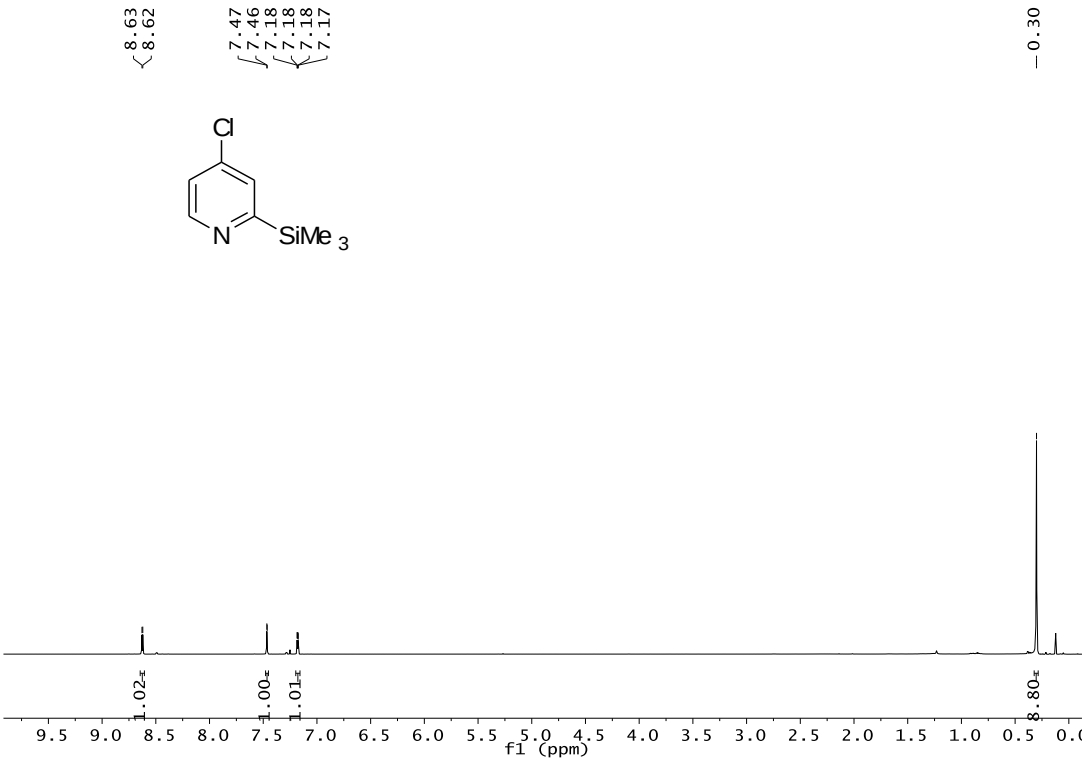
^{1}H NMR (700 MHz, $CDCl_3$) - 242



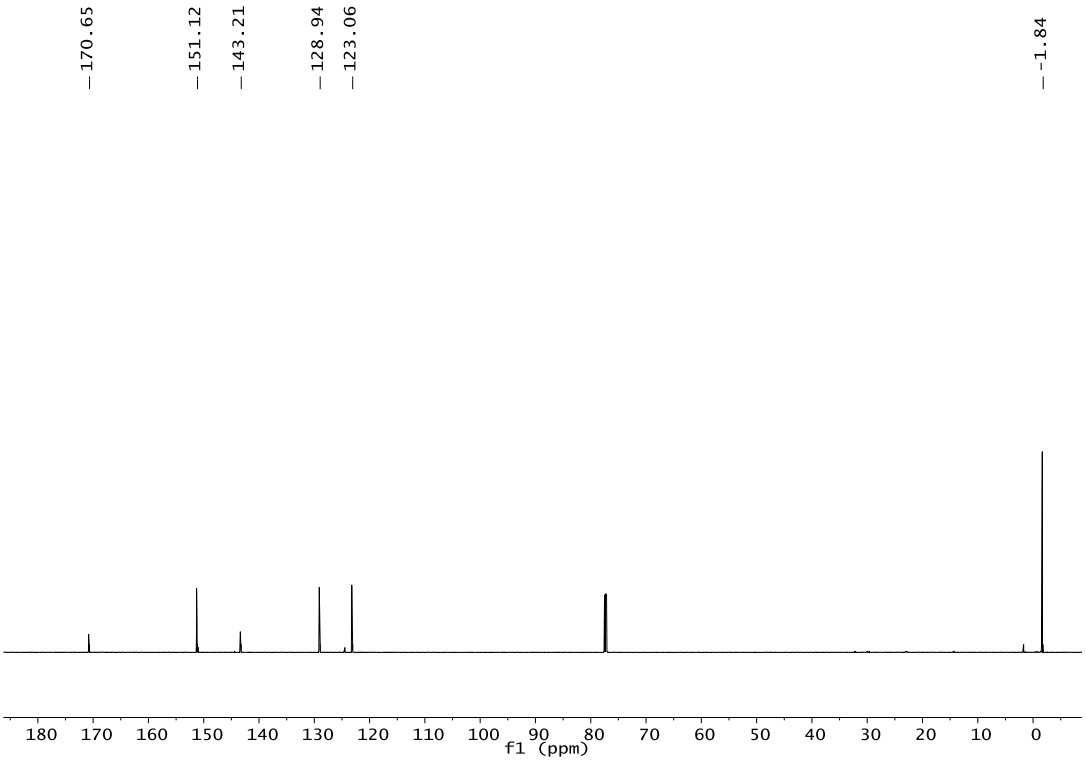
^{13}C NMR (176 MHz, $CDCl_3$) - 242



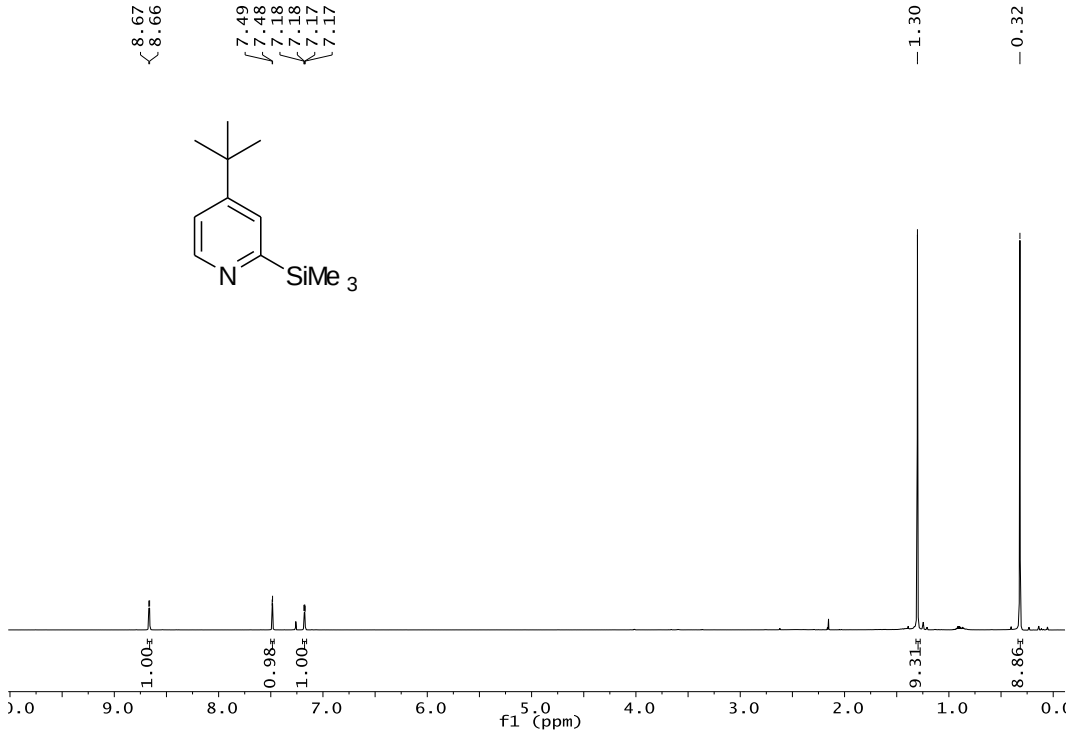
^{1}H NMR (700 MHz, $CDCl_3$) - 254



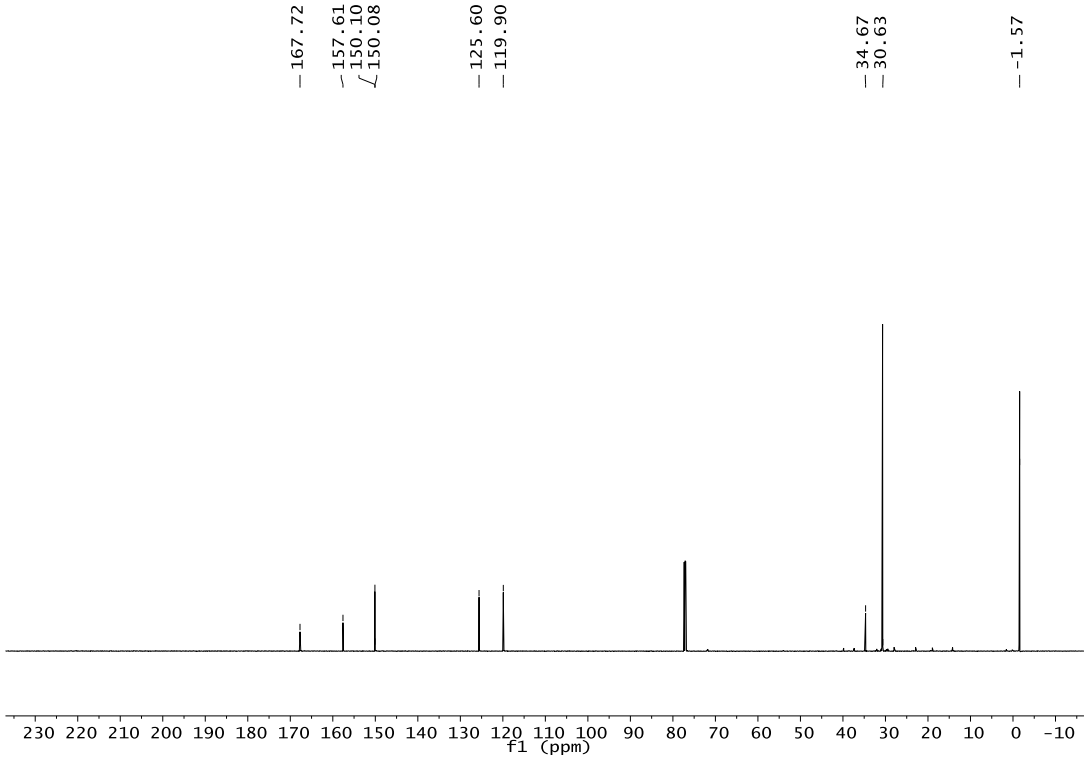
^{13}C NMR (176 MHz, $CDCl_3$) - 254



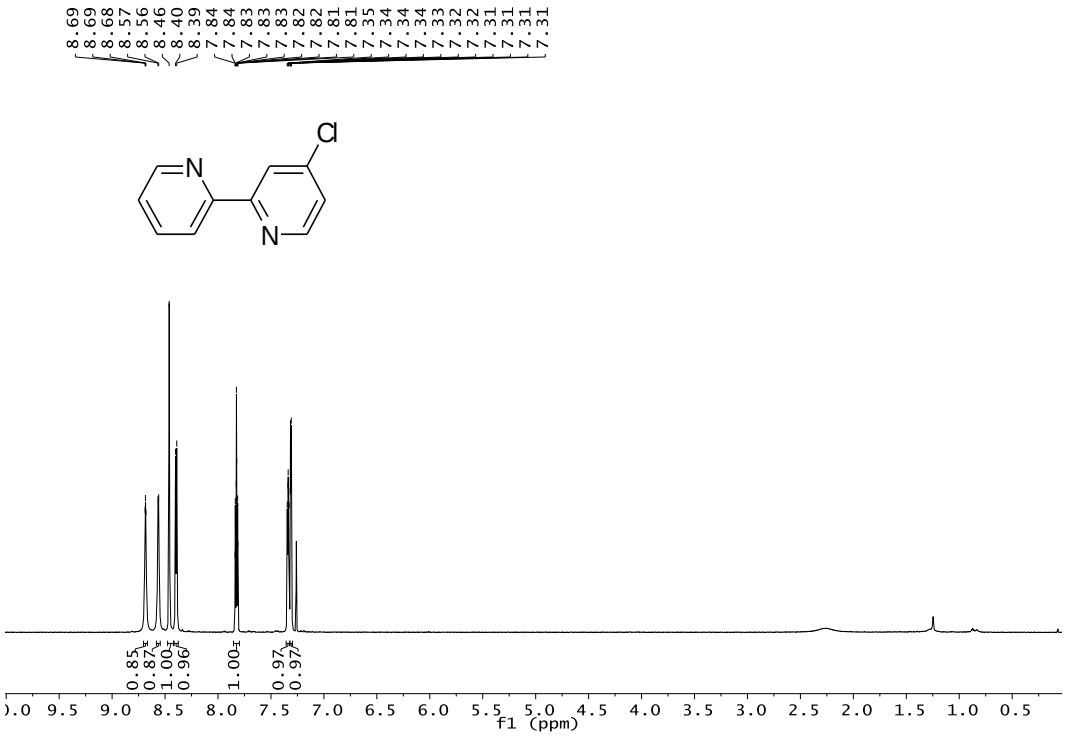
^{1}H NMR (700 MHz, $CDCl_3$) - 260



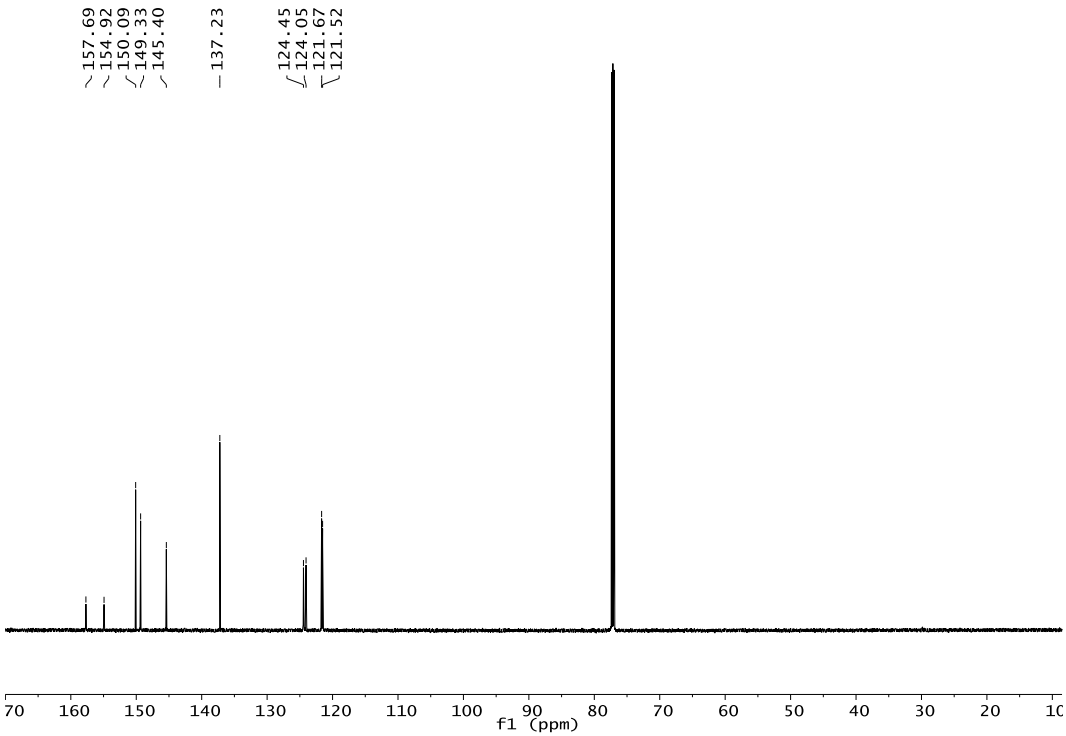
^{13}C NMR (176 MHz, $CDCl_3$) - 260



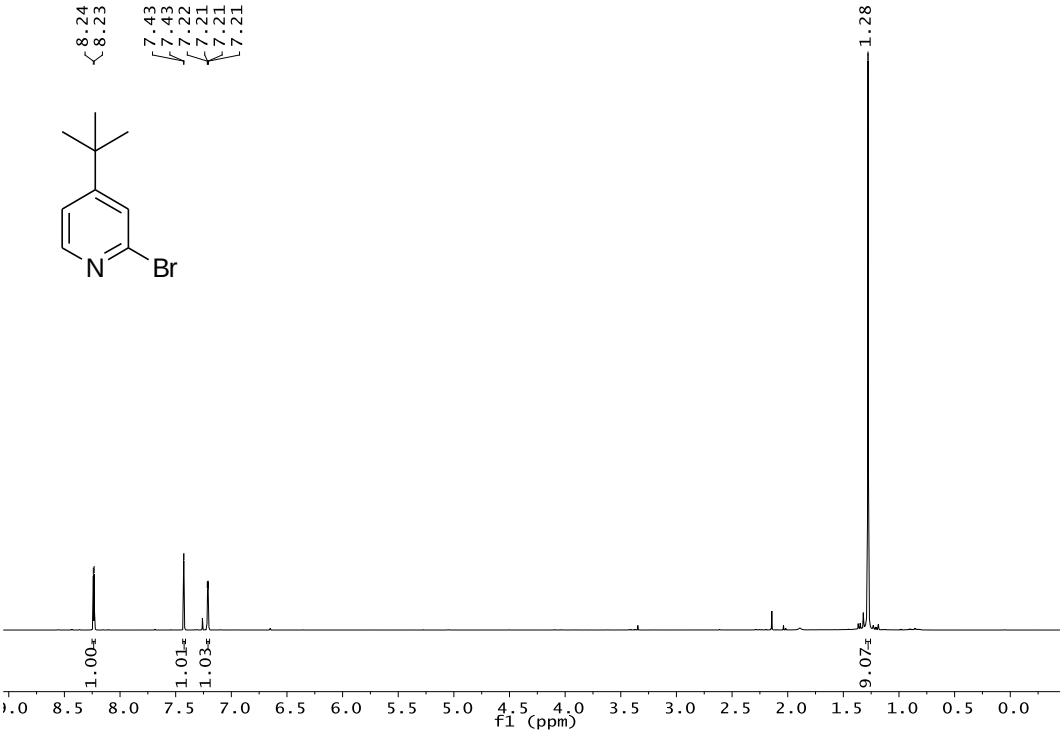
^{1}H NMR (700 MHz, $CDCl_3$) - 255



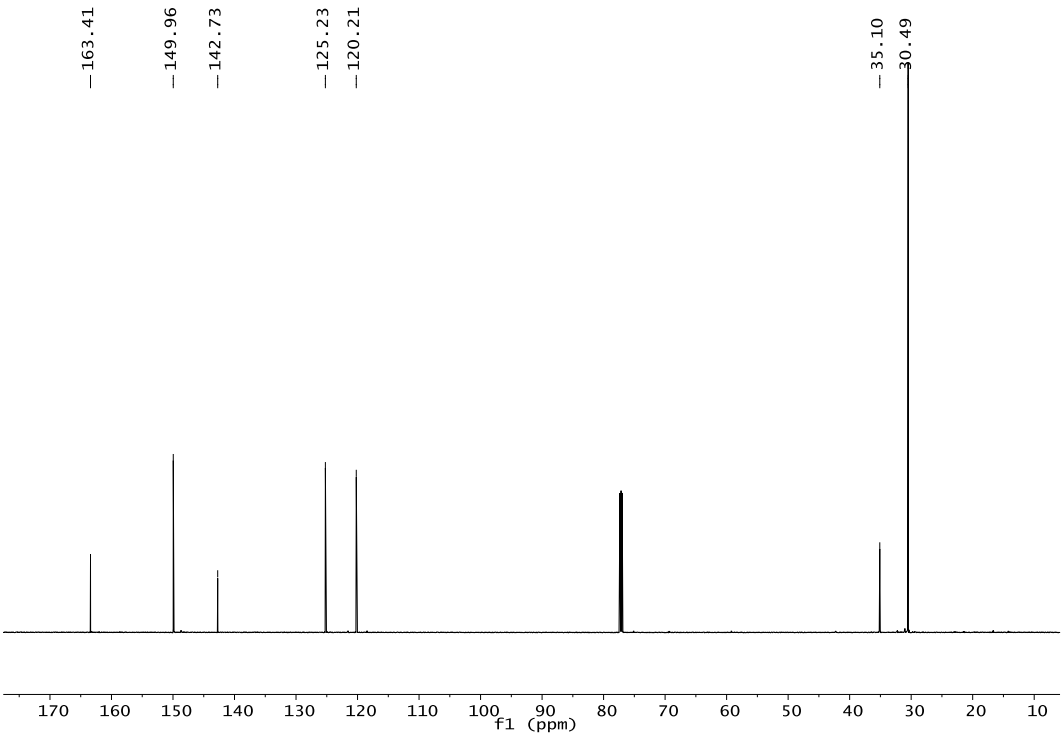
^{13}C NMR (176 MHz, $CDCl_3$) - 255



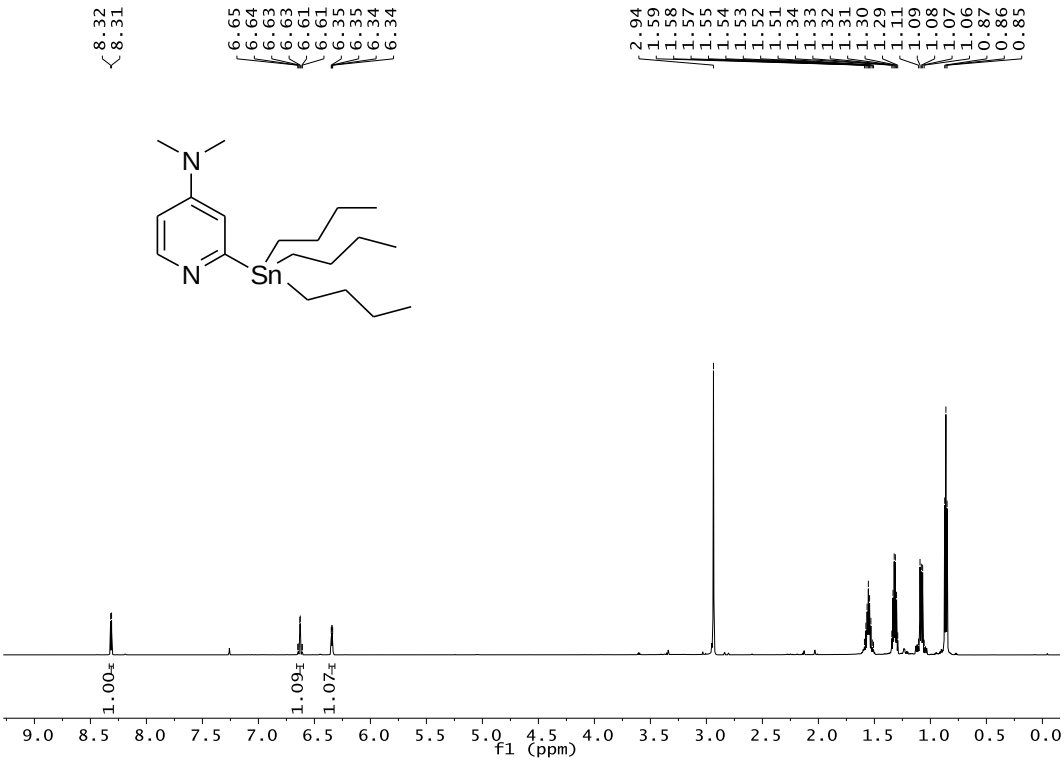
^{1}H NMR (700 MHz, $CDCl_3$) - 252



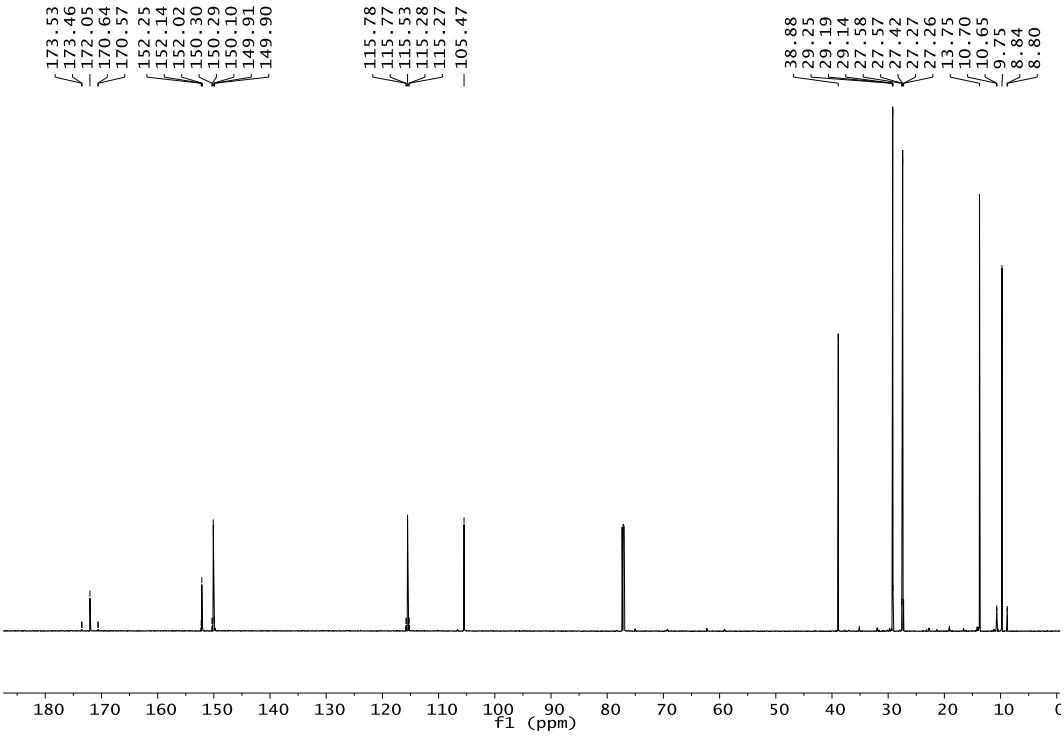
^{13}C NMR (176 MHz, $CDCl_3$) - 252



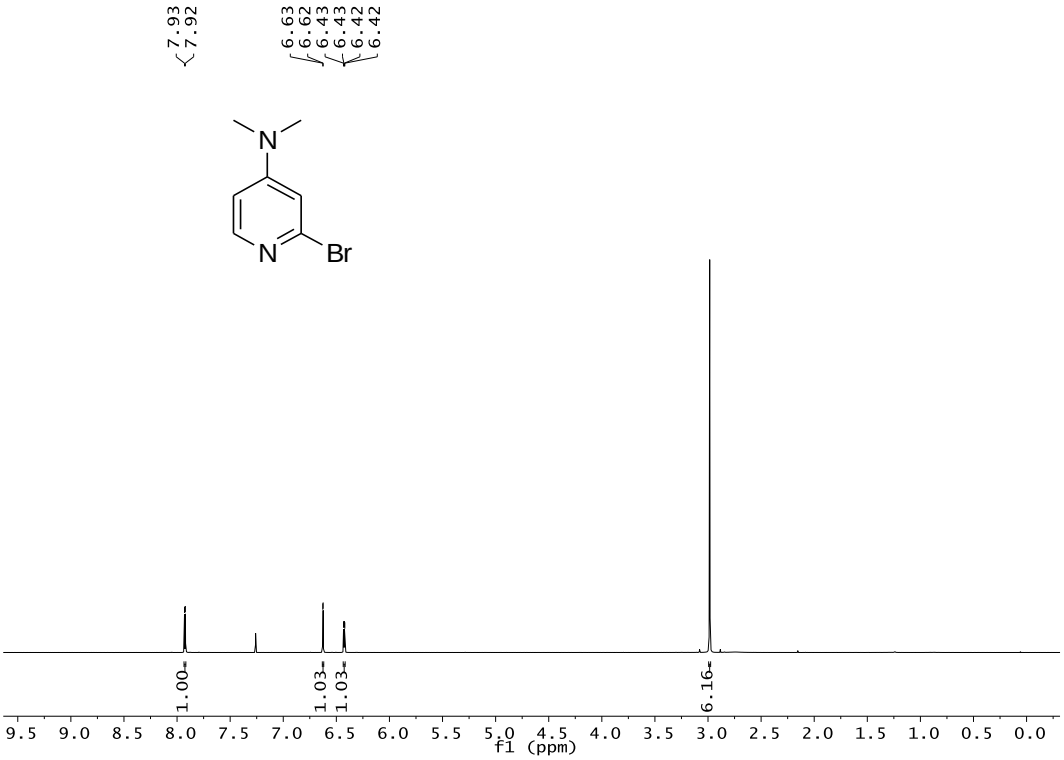
^{1}H NMR (700 MHz, $CDCl_3$) - 266



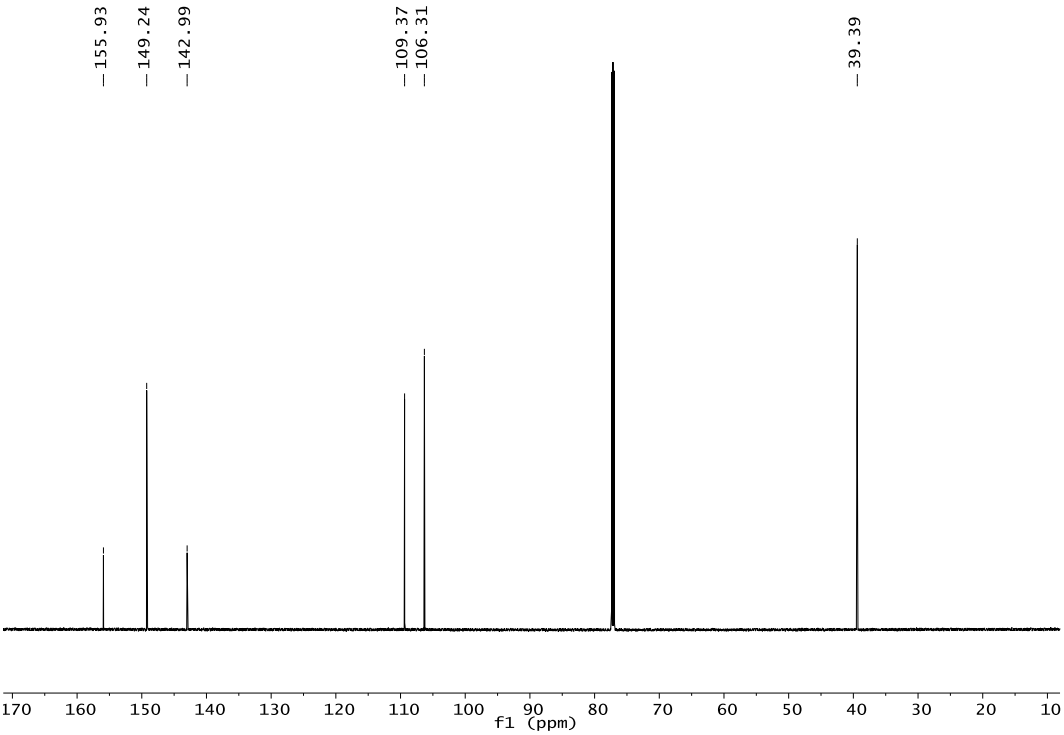
^{13}C NMR (176 MHz, $CDCl_3$) - 266



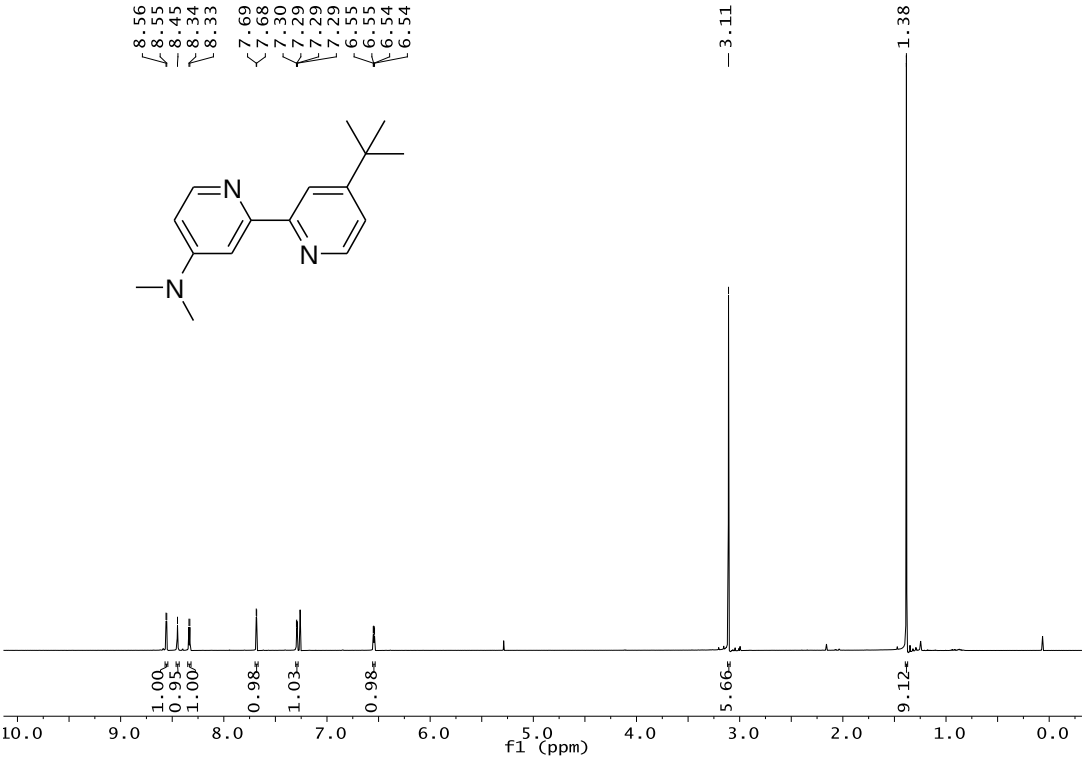
^{1}H NMR (700 MHz, $CDCl_3$) - 267



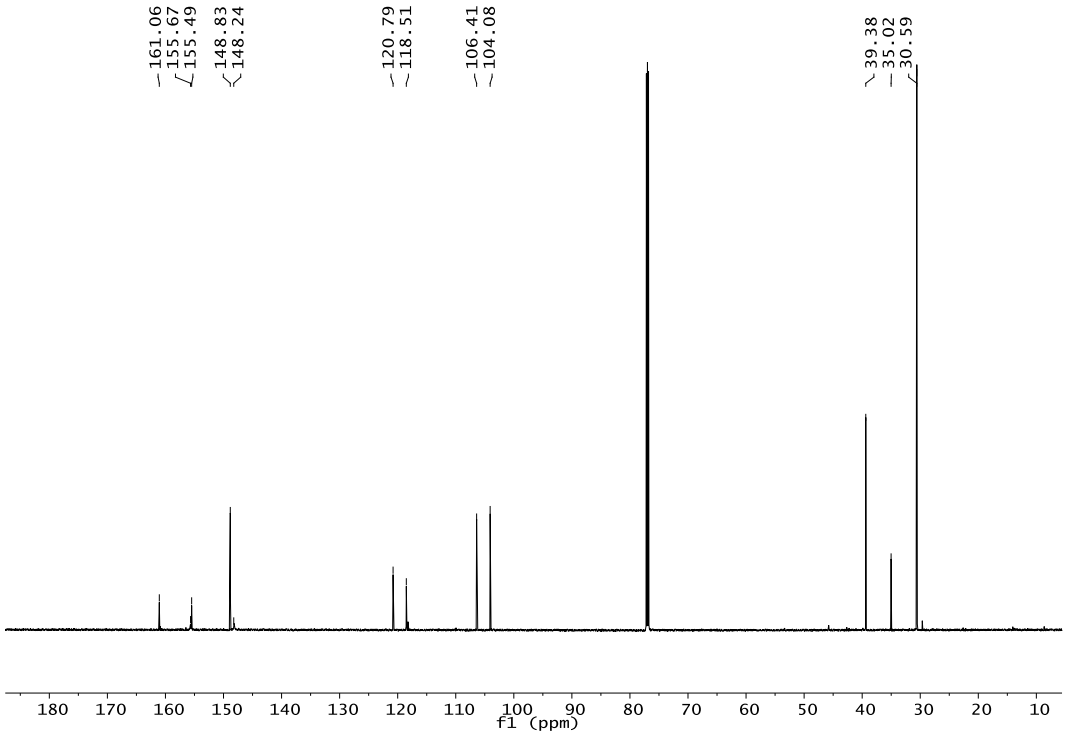
^{13}C NMR (176 MHz, $CDCl_3$) - 267



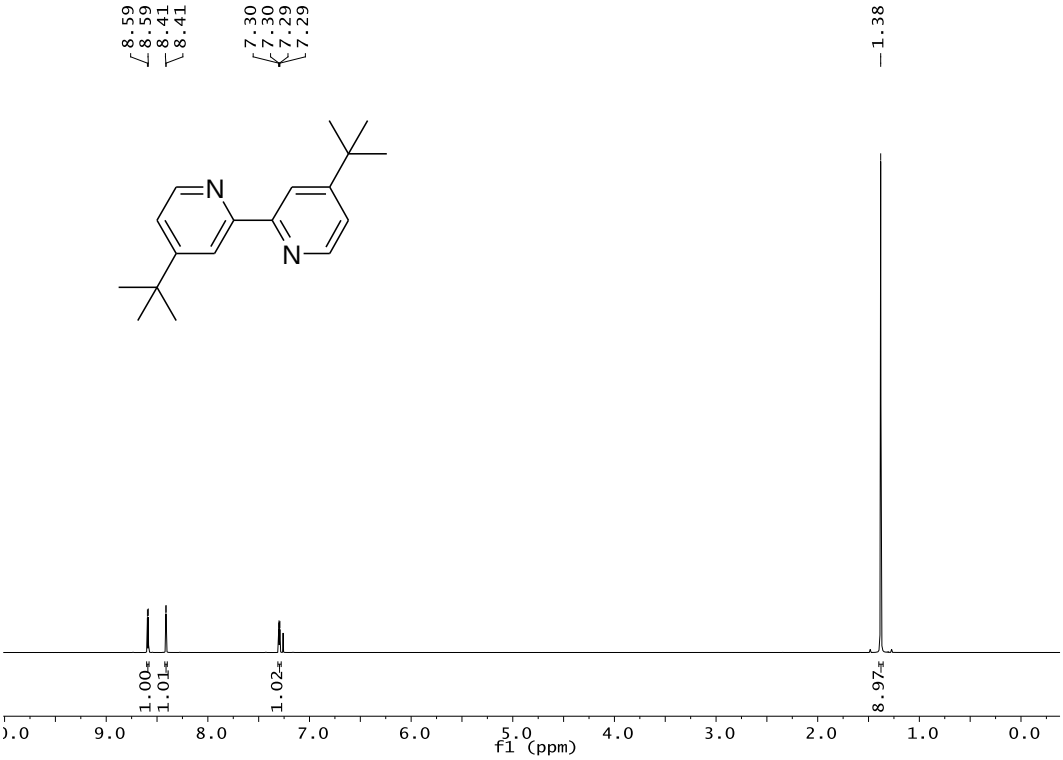
^{1}H NMR (700 MHz, $CDCl_3$) - 250



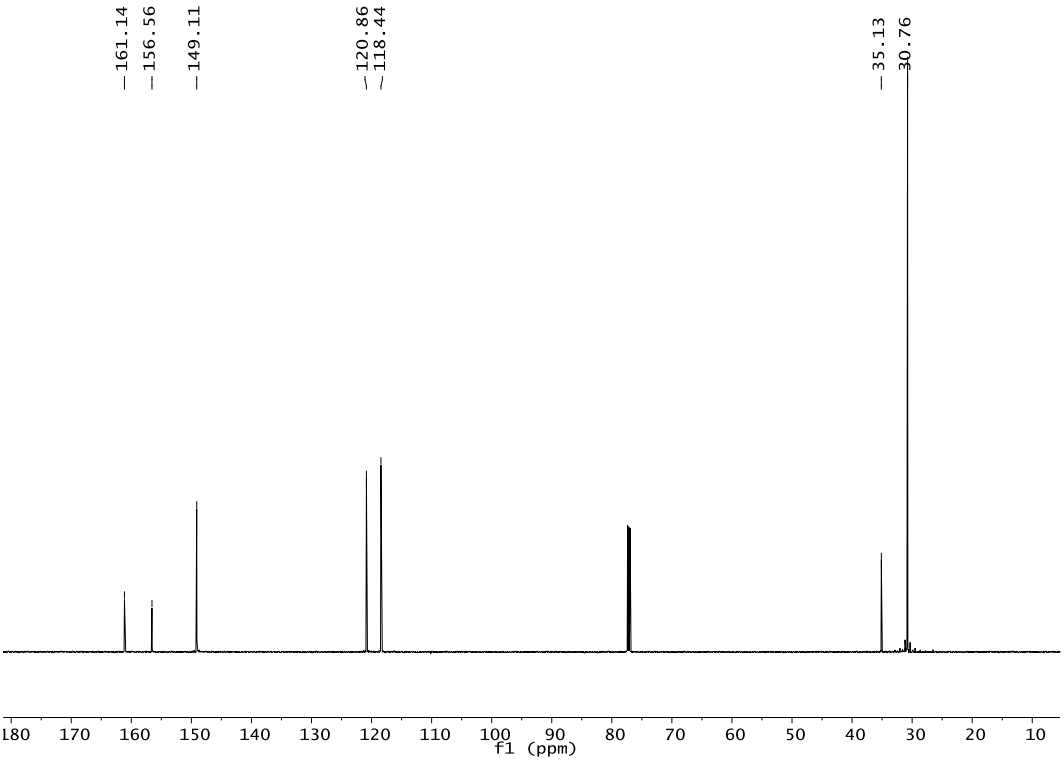
^{13}C NMR (176 MHz, $CDCl_3$) - 250



^{1}H NMR (600 MHz, $CDCl_3$) - 22

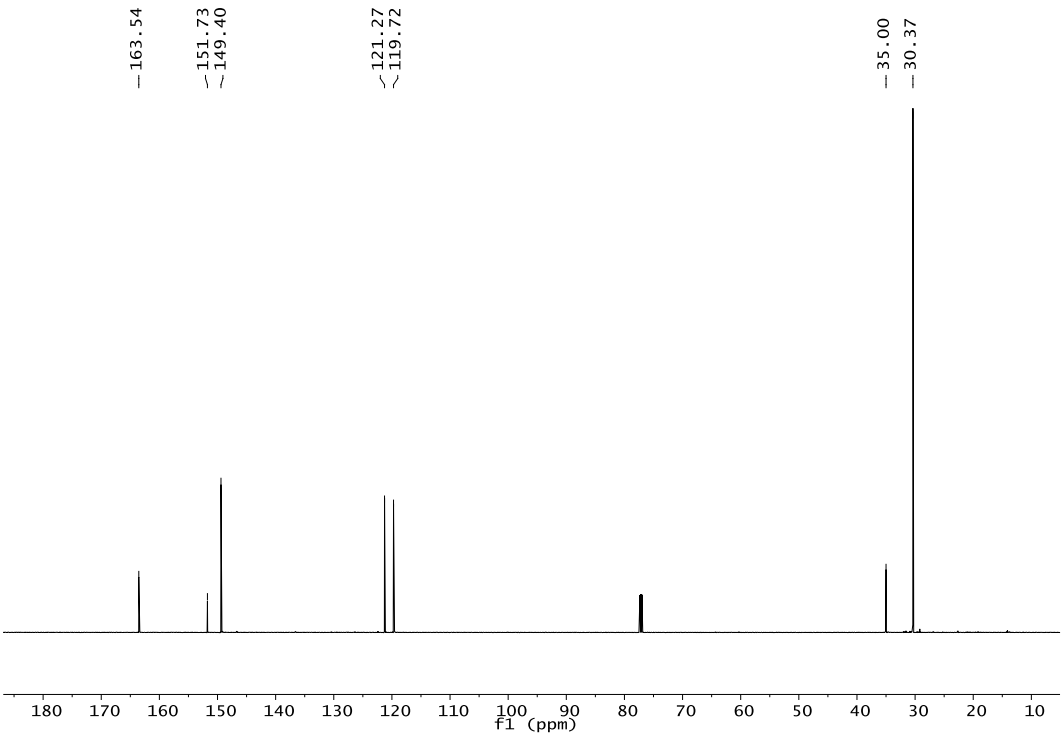


^{13}C NMR (151 MHz, $CDCl_3$)- 22

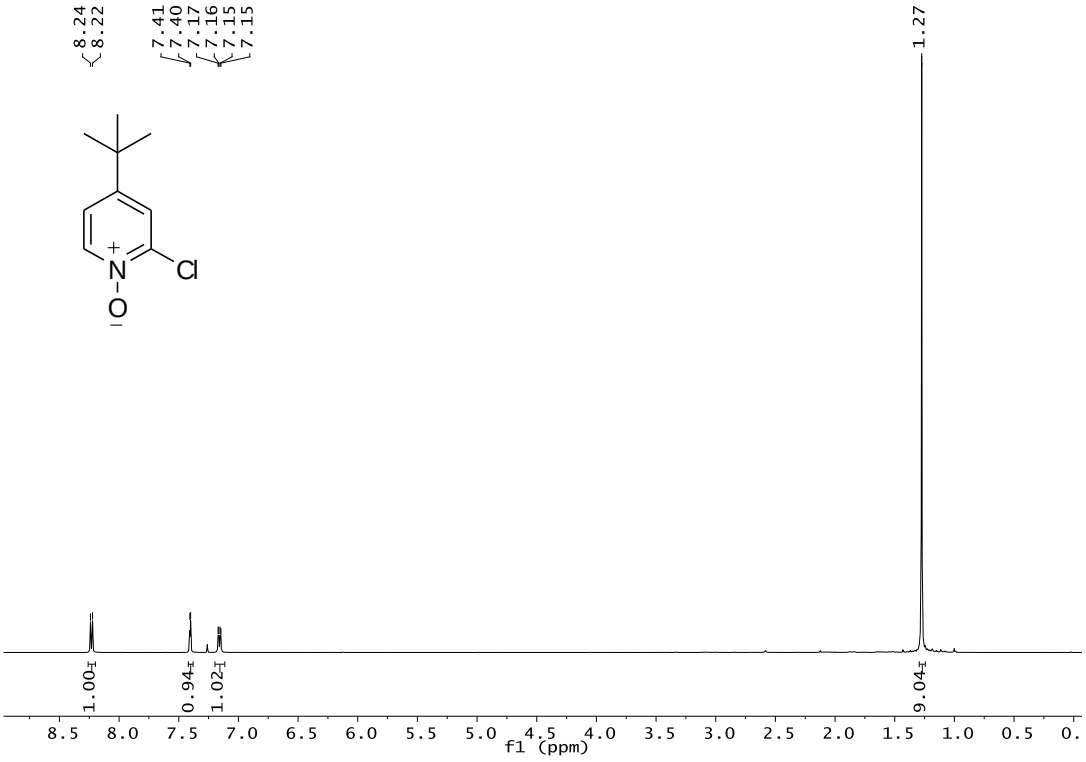


^{1}H NMR (700 MHz, $CDCl_3$) - 265

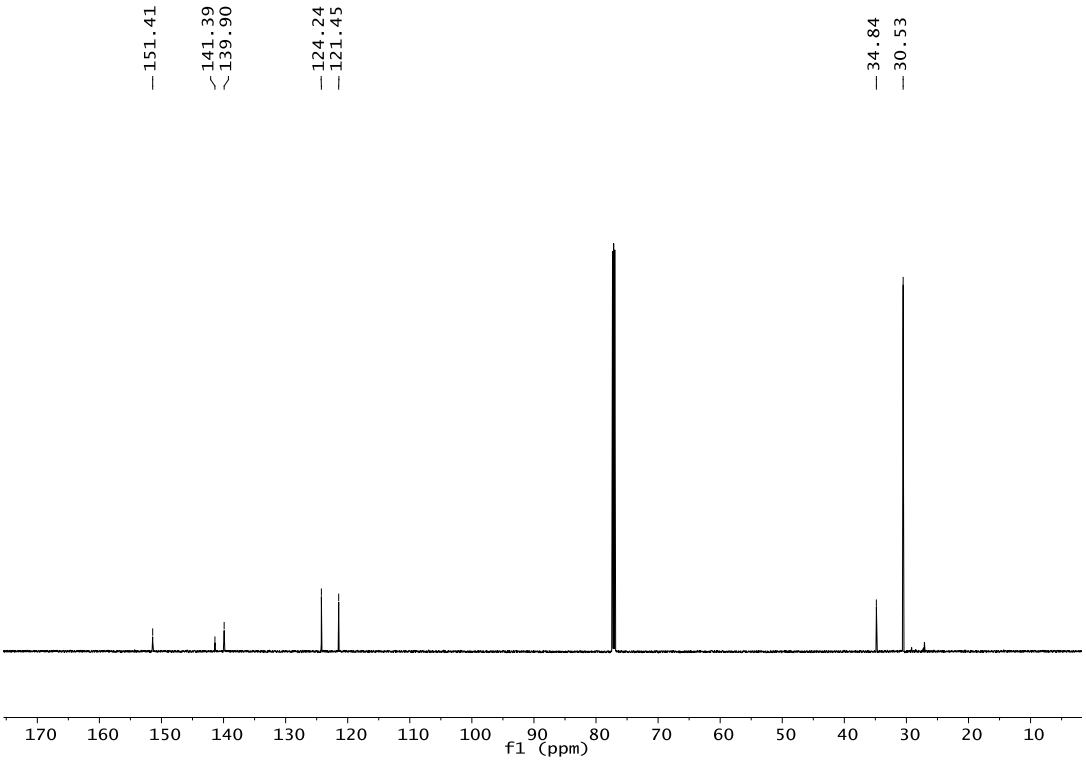
^{13}C NMR (176 MHz, $CDCl_3$) - 265



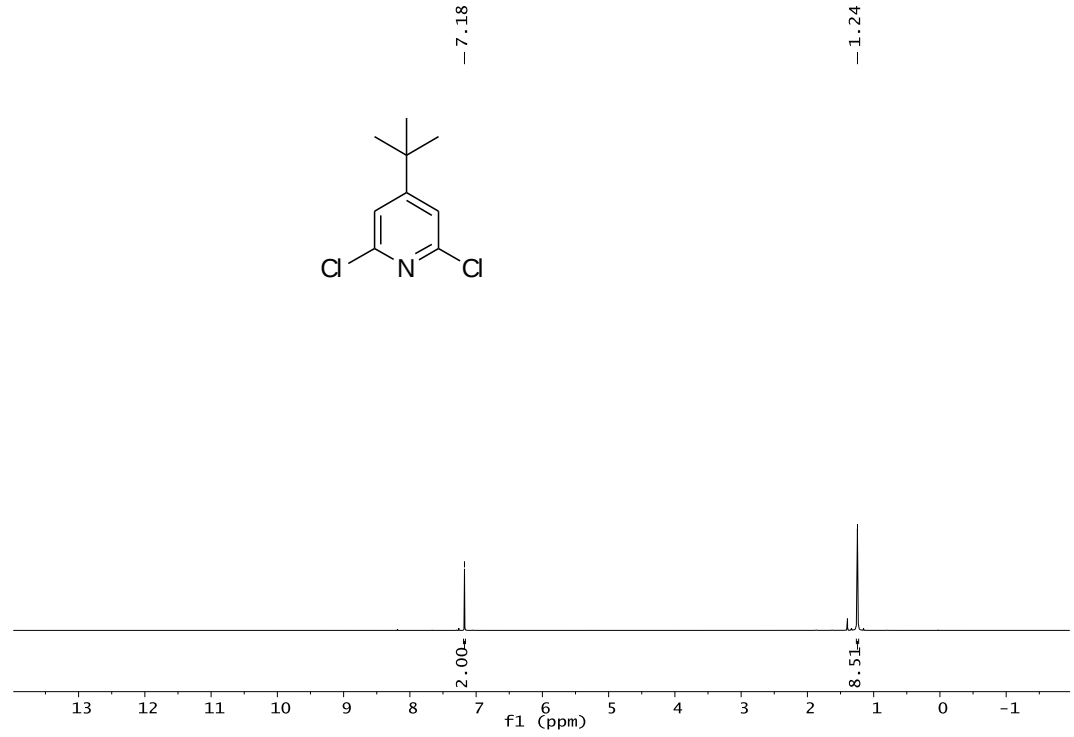
^{1}H NMR (700 MHz, $CDCl_3$) - 274



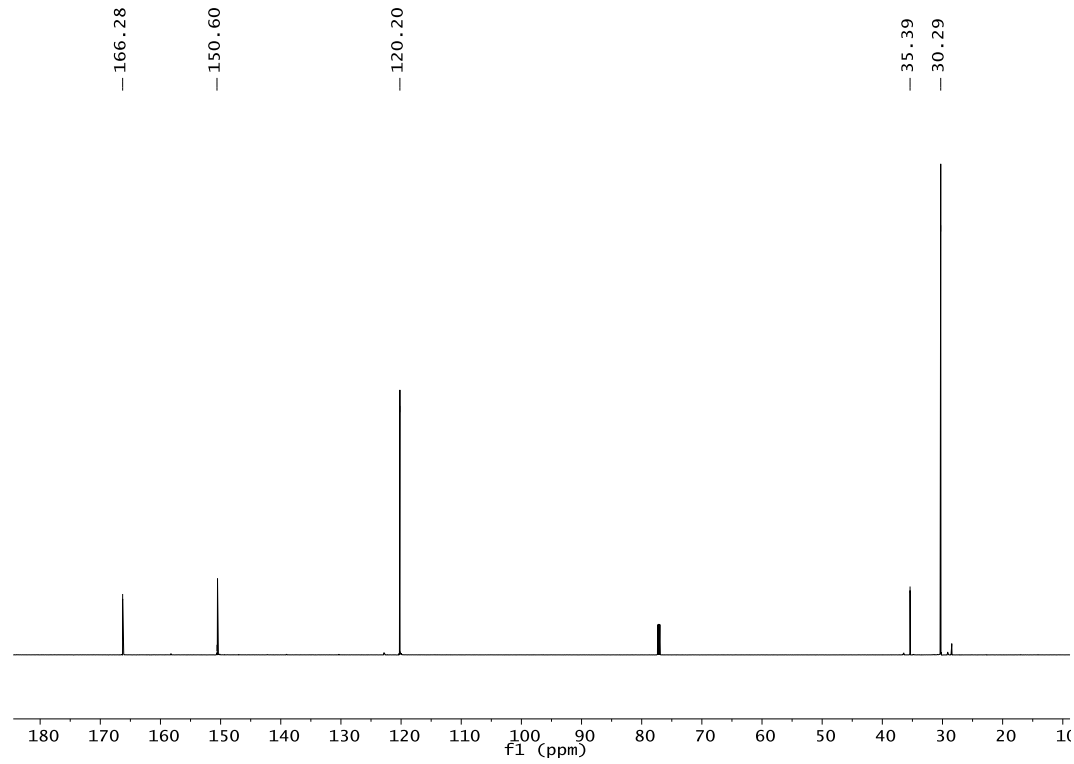
^{13}C NMR (176 MHz, $CDCl_3$) - 274



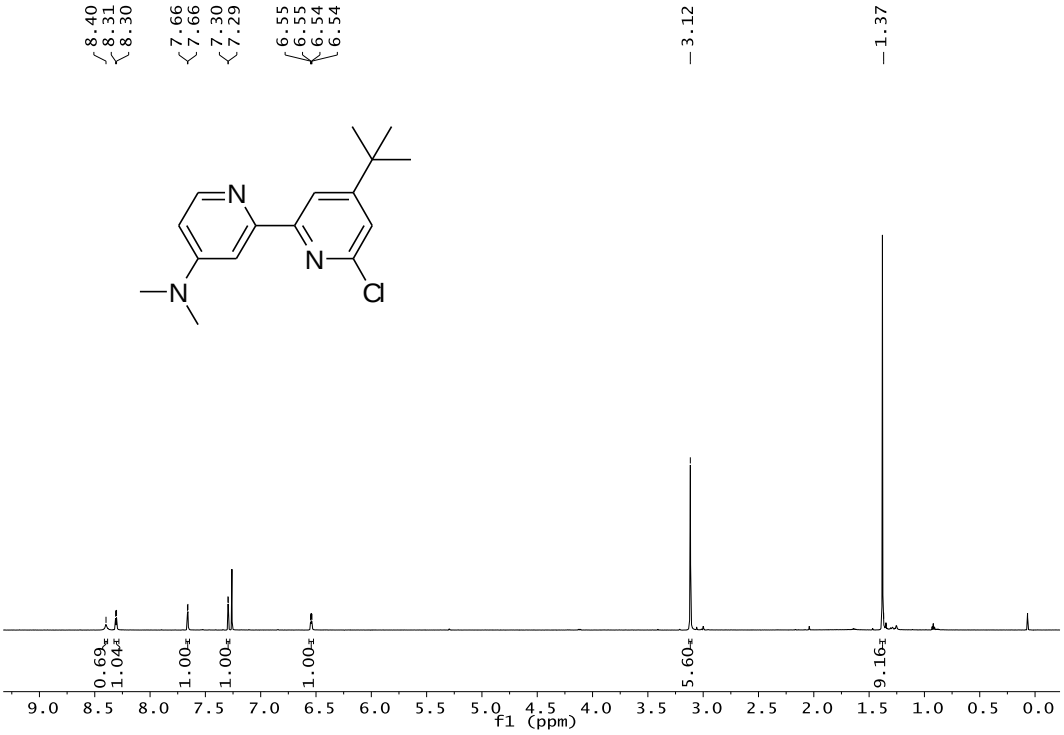
^{1}H NMR (700 MHz, $CDCl_3$) – 276



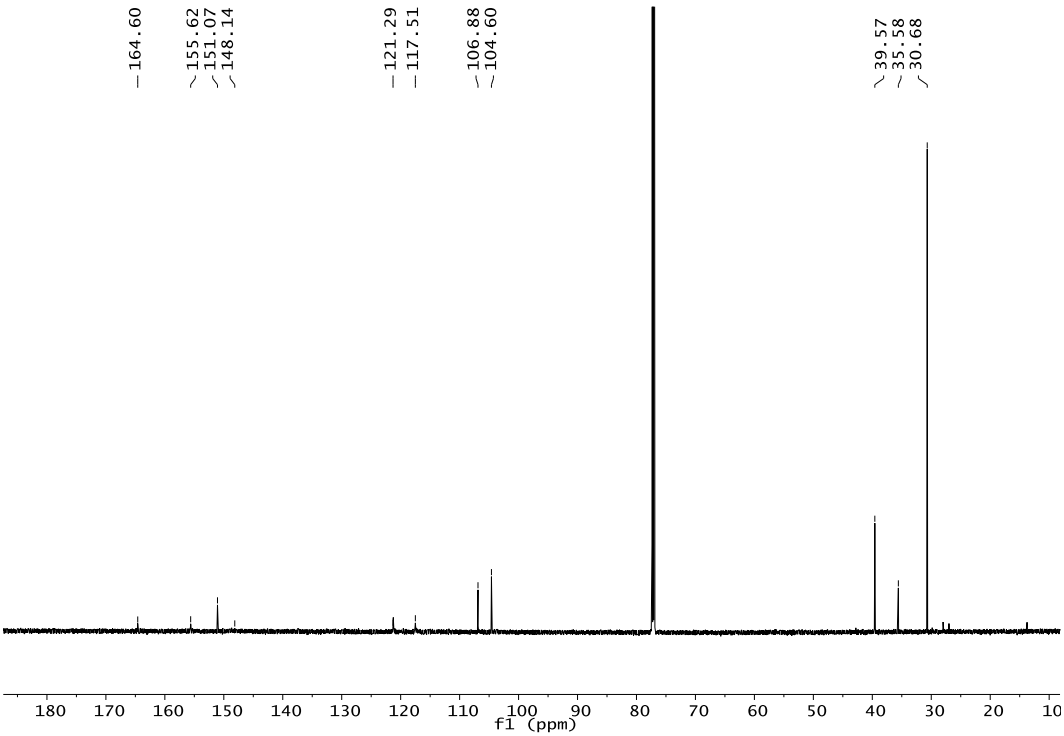
^{13}C NMR (176 MHz, $CDCl_3$) - 276



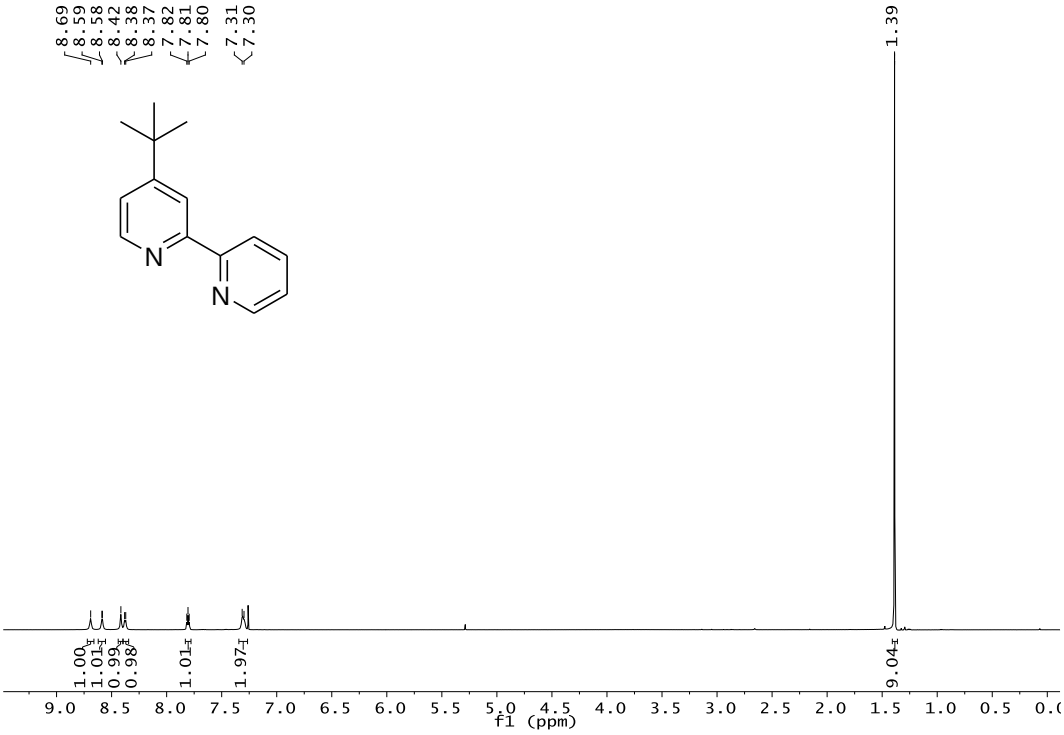
^{1}H NMR (700 MHz, $CDCl_3$) - 277



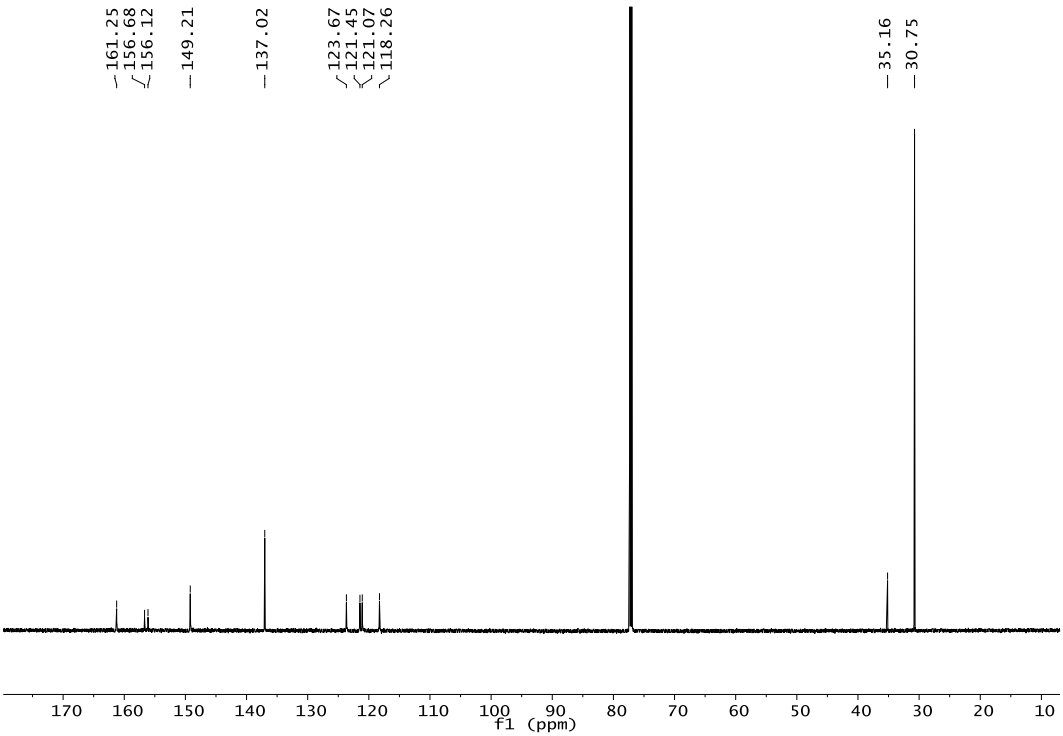
^{13}C NMR (176 MHz, $CDCl_3$) - 277



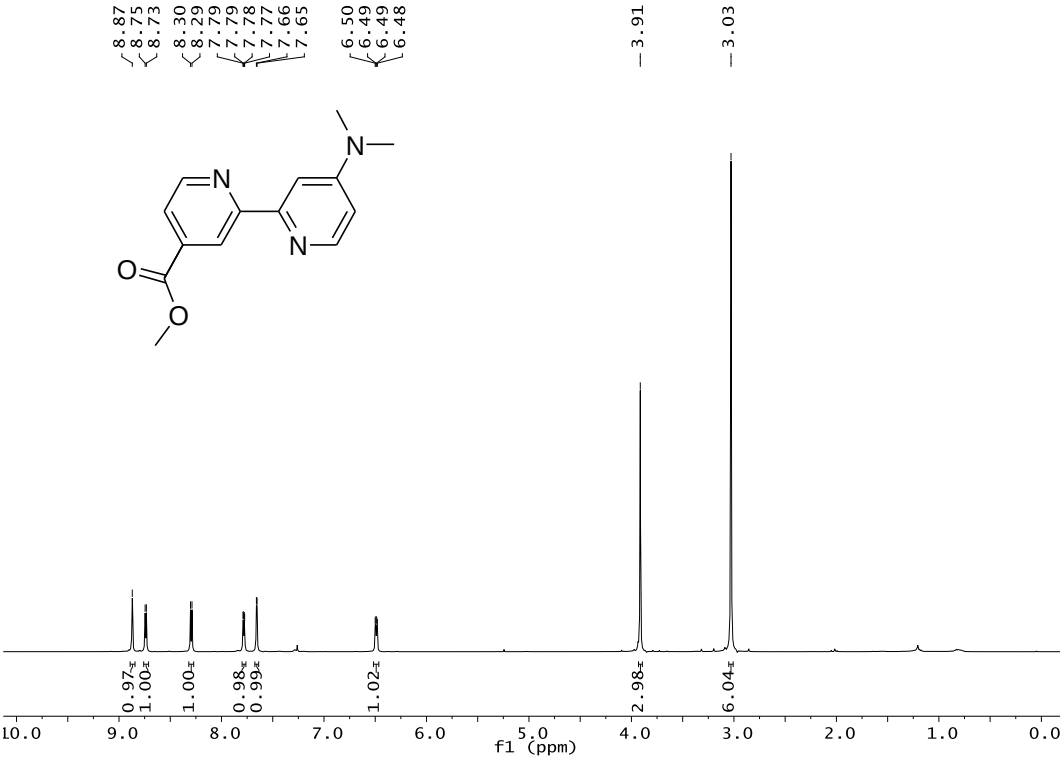
^{1}H NMR (700 MHz, $CDCl_3$)- 281



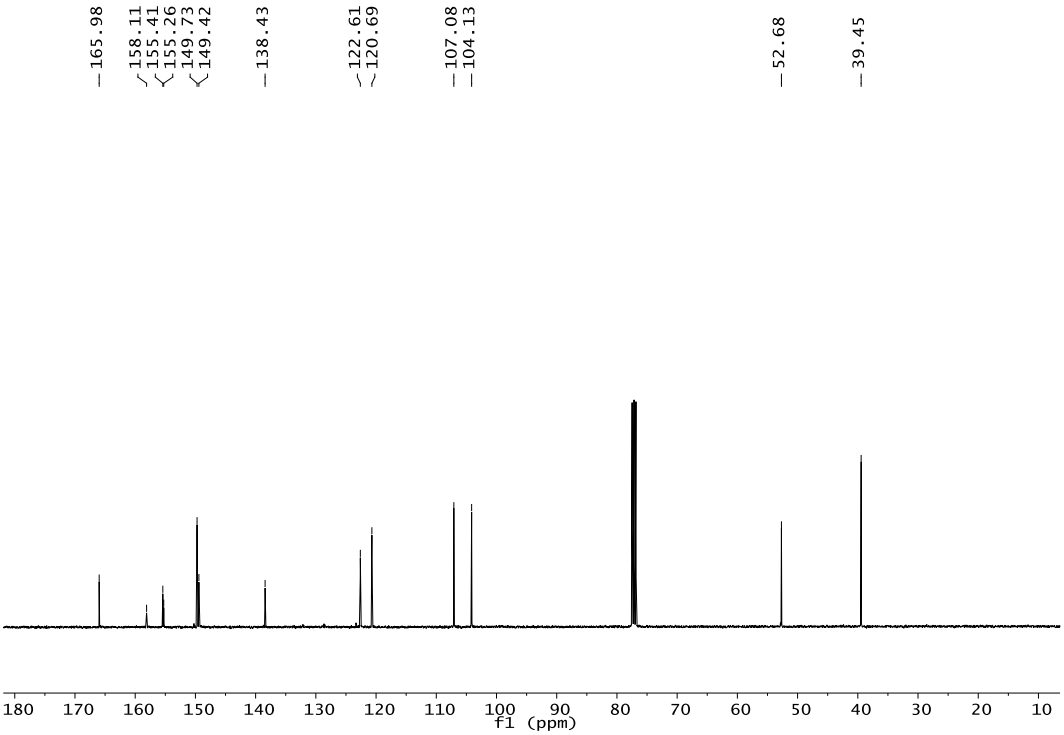
^{13}C NMR (176 MHz, $CDCl_3$)- 281



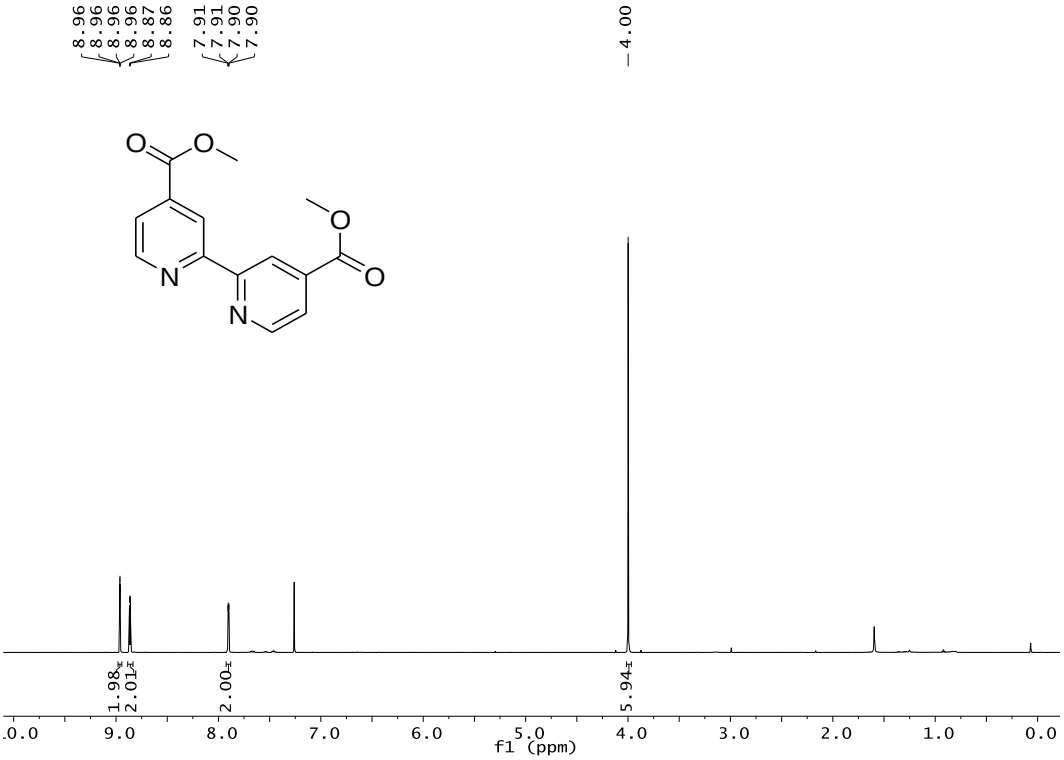
^{1}H NMR (700 MHz, $CDCl_3$) - 285



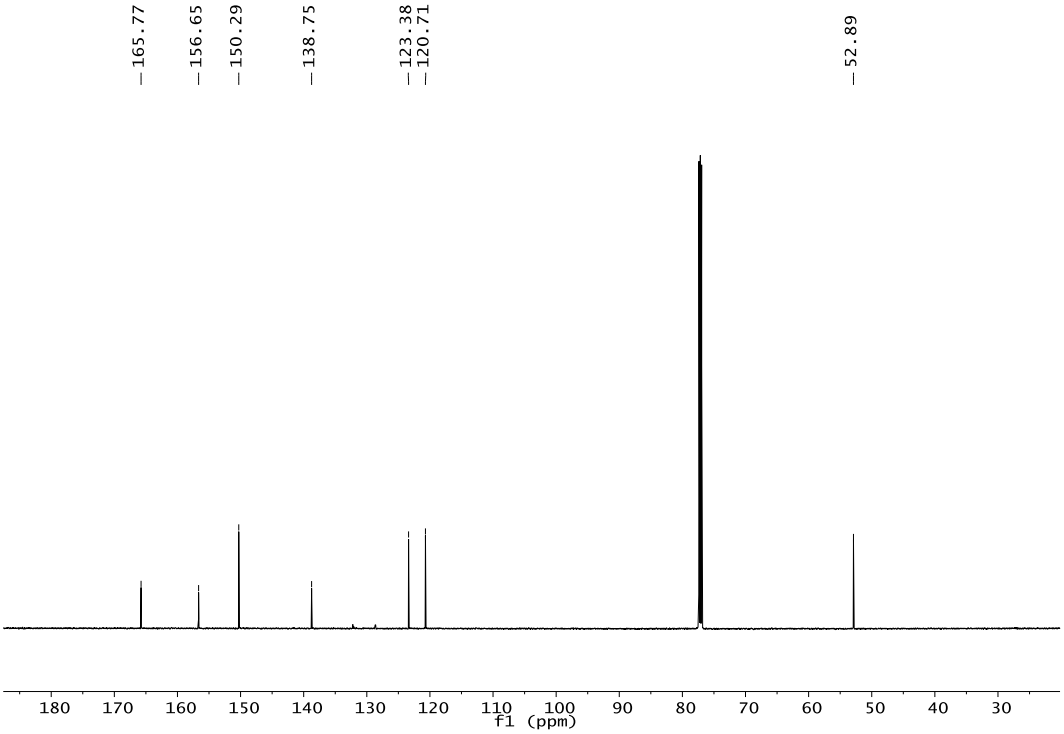
^{13}C NMR (176 MHz, $CDCl_3$) - 285



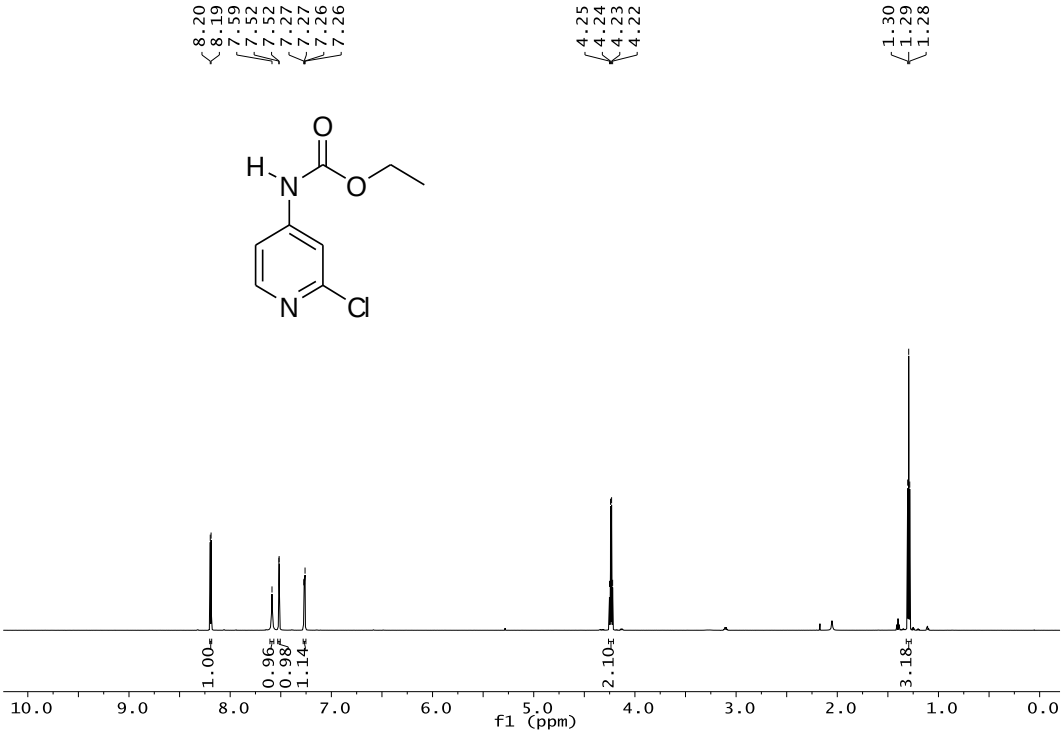
^{1}H NMR (700 MHz, $CDCl_3$) – 286



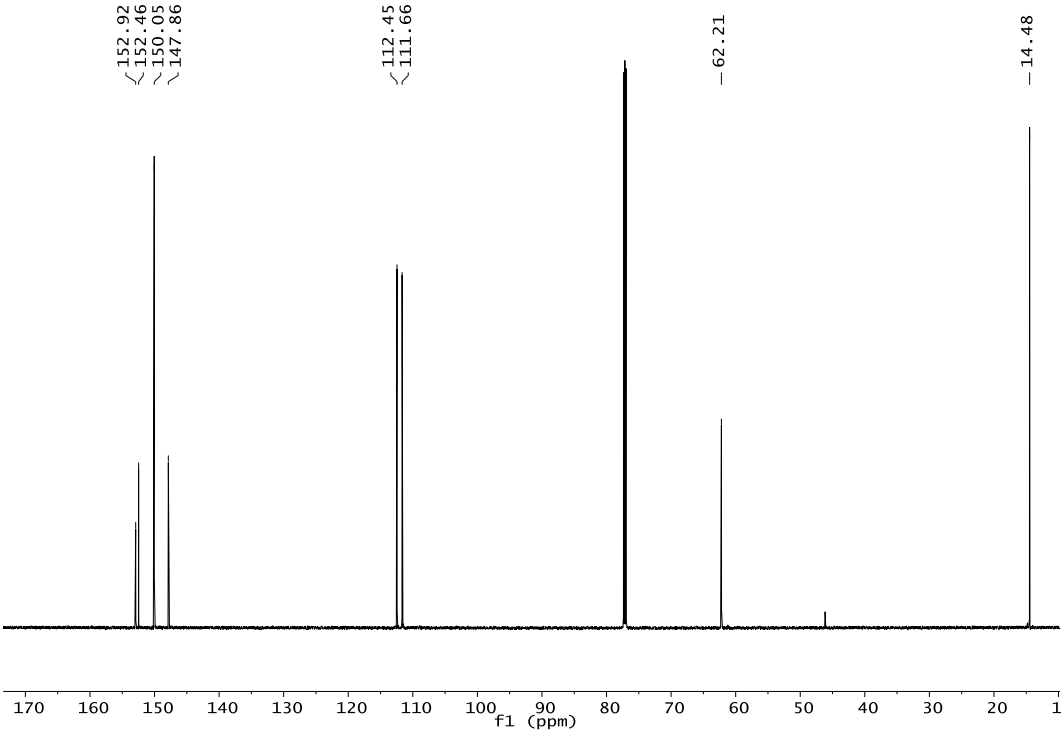
^{13}C NMR (176 MHz, $CDCl_3$) - 286



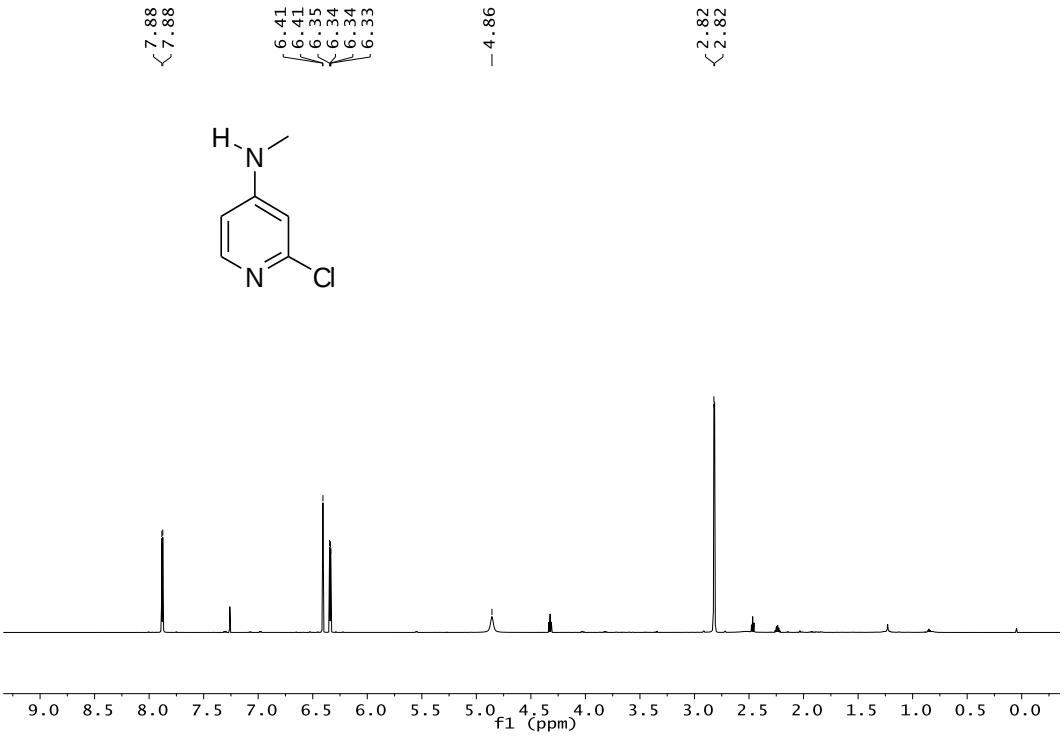
^{1}H NMR (700 MHz, $CDCl_3$) - 292



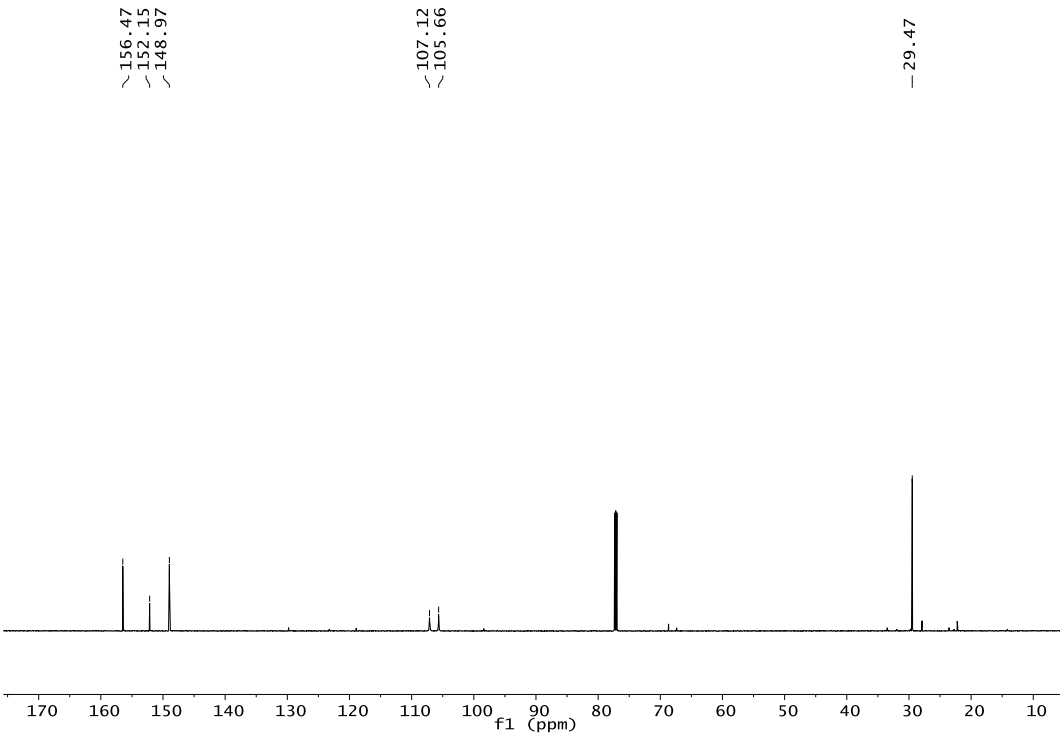
^{13}C NMR (176 MHz, $CDCl_3$) - 292



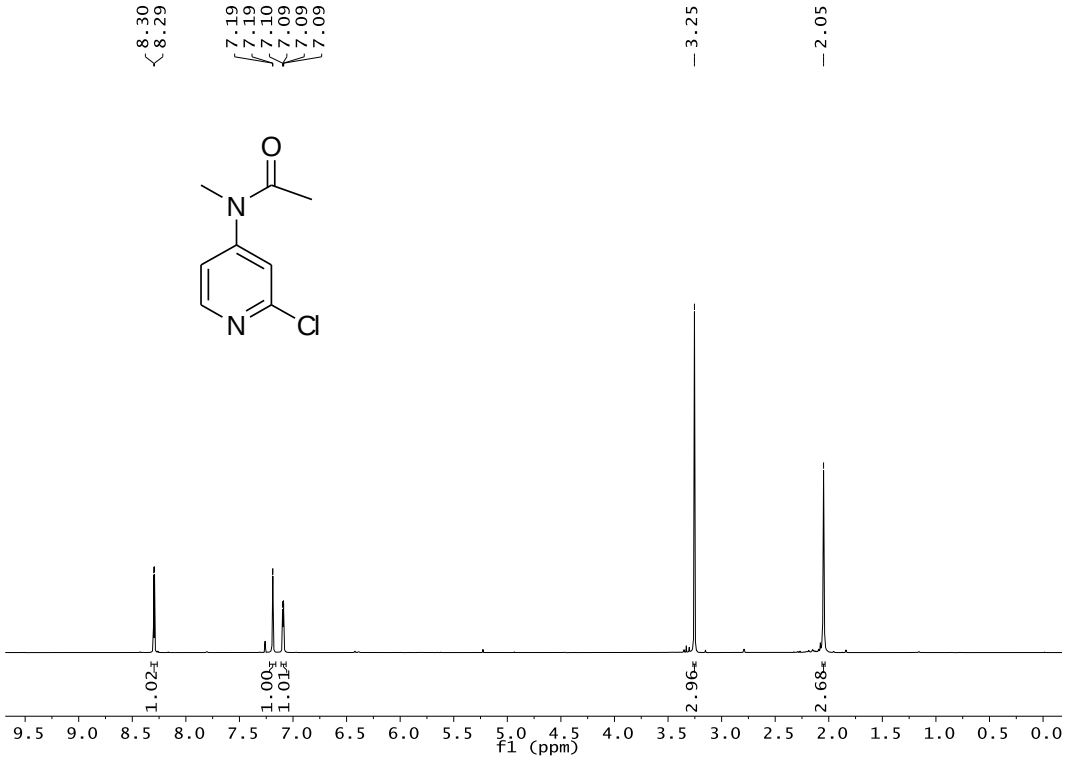
^{1}H NMR (700 MHz, $CDCl_3$) - 293



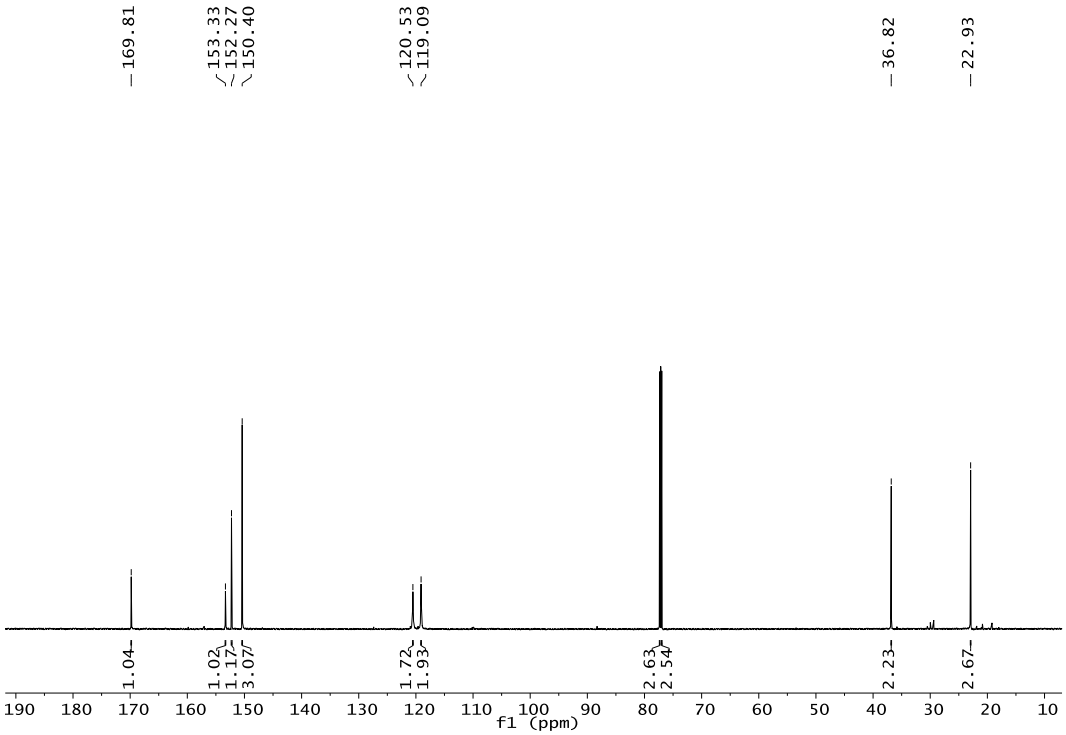
^{13}C NMR (176 MHz, $CDCl_3$) - 293



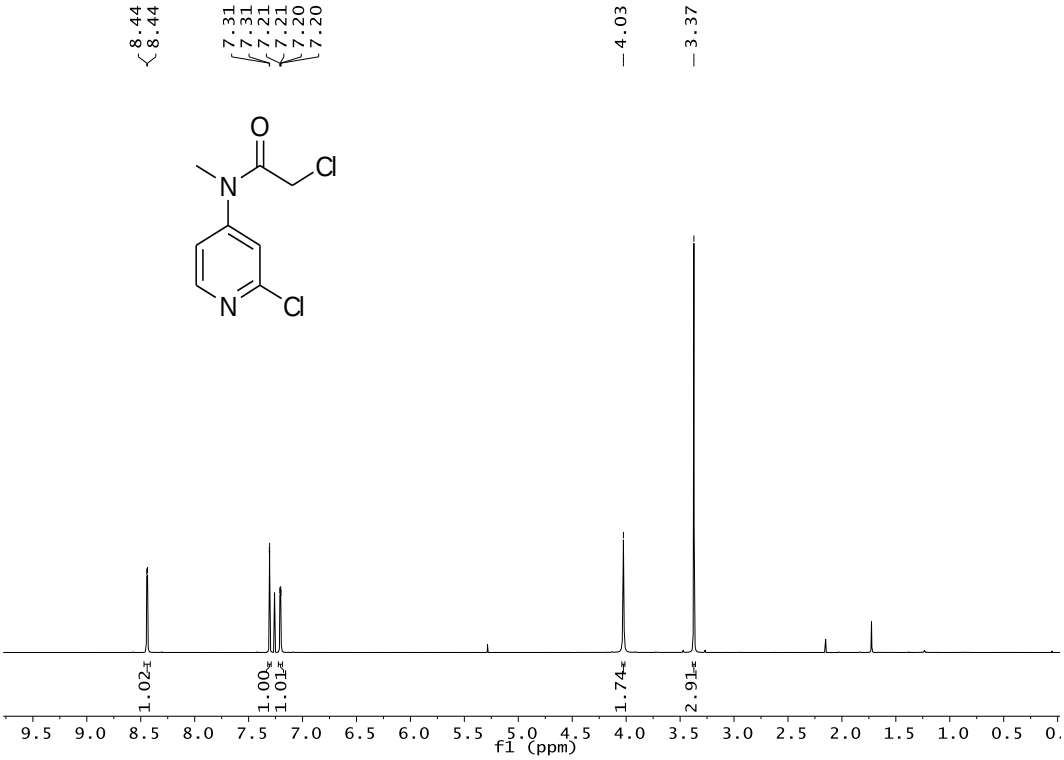
^{1}H NMR (700 MHz, $CDCl_3$) - 294



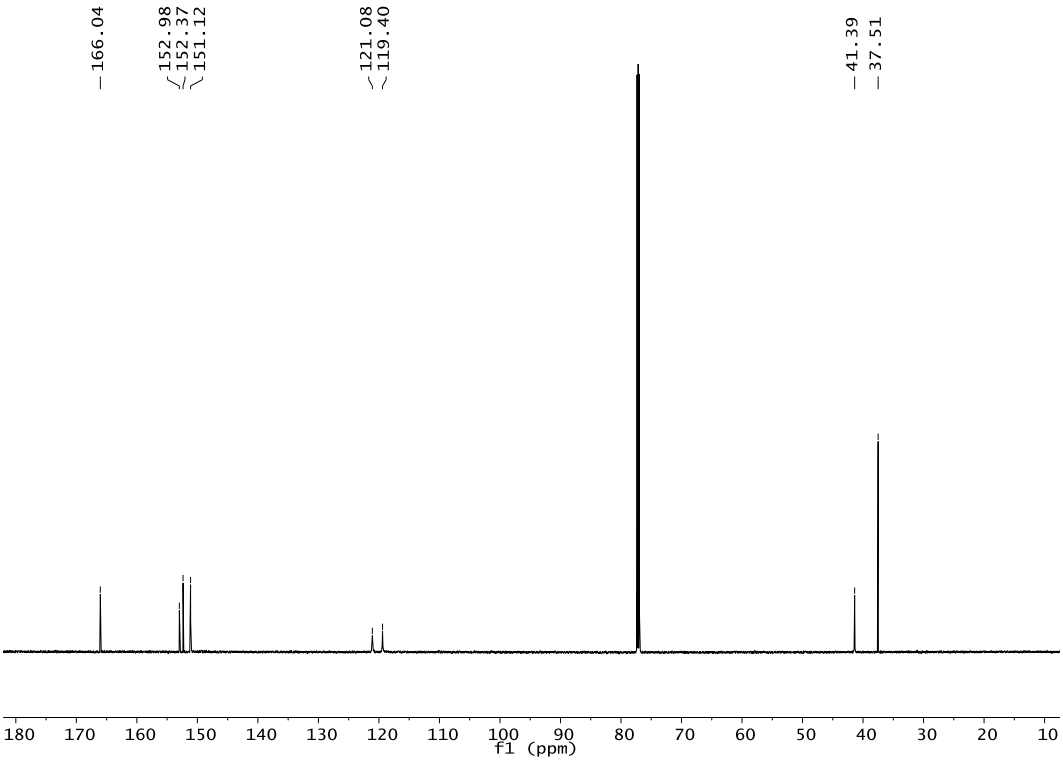
^{13}C NMR (176 MHz, $CDCl_3$) - 294



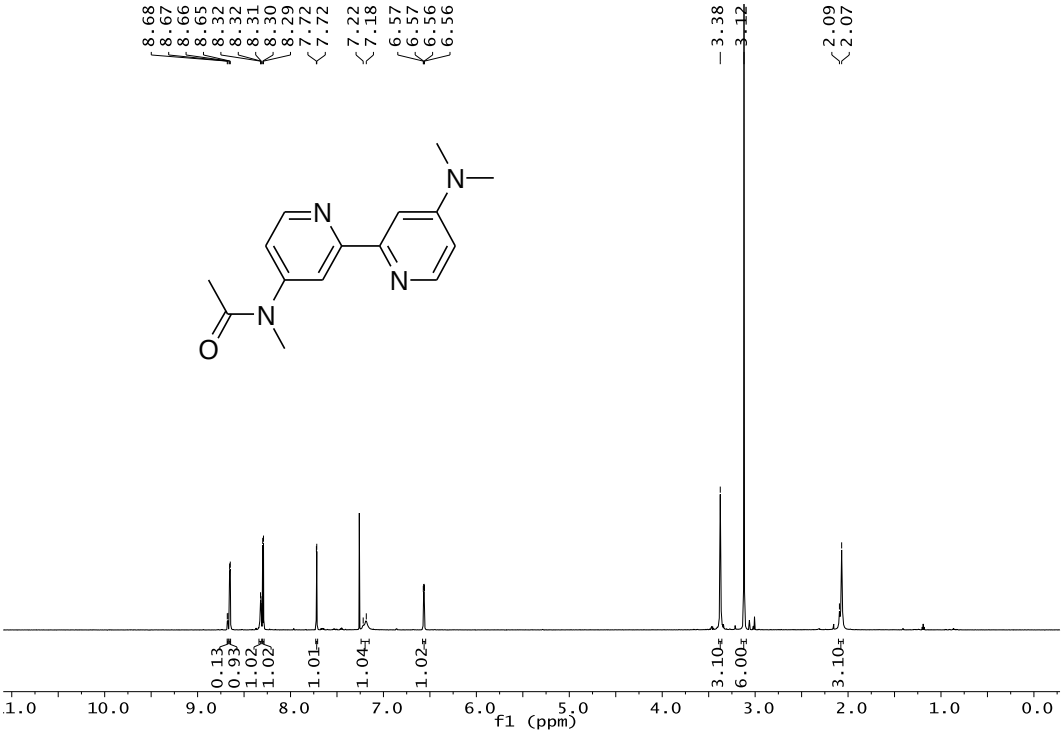
^{1}H NMR (700 MHz, $CDCl_3$) - 295



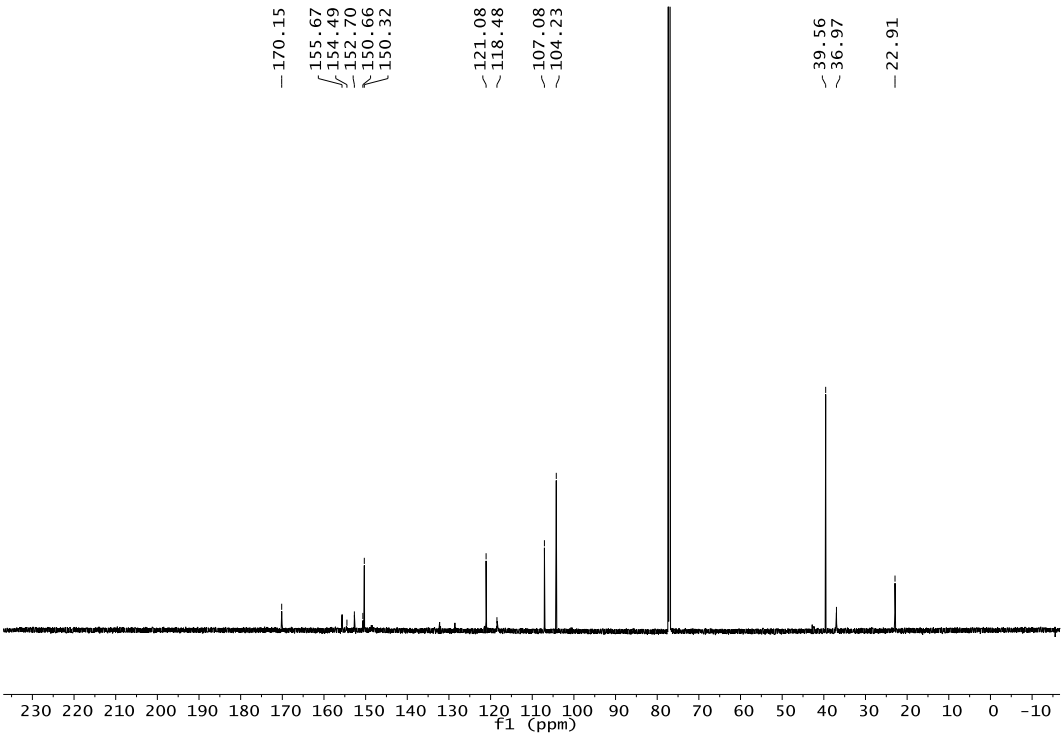
^{13}C NMR (176 MHz, $CDCl_3$) - 295



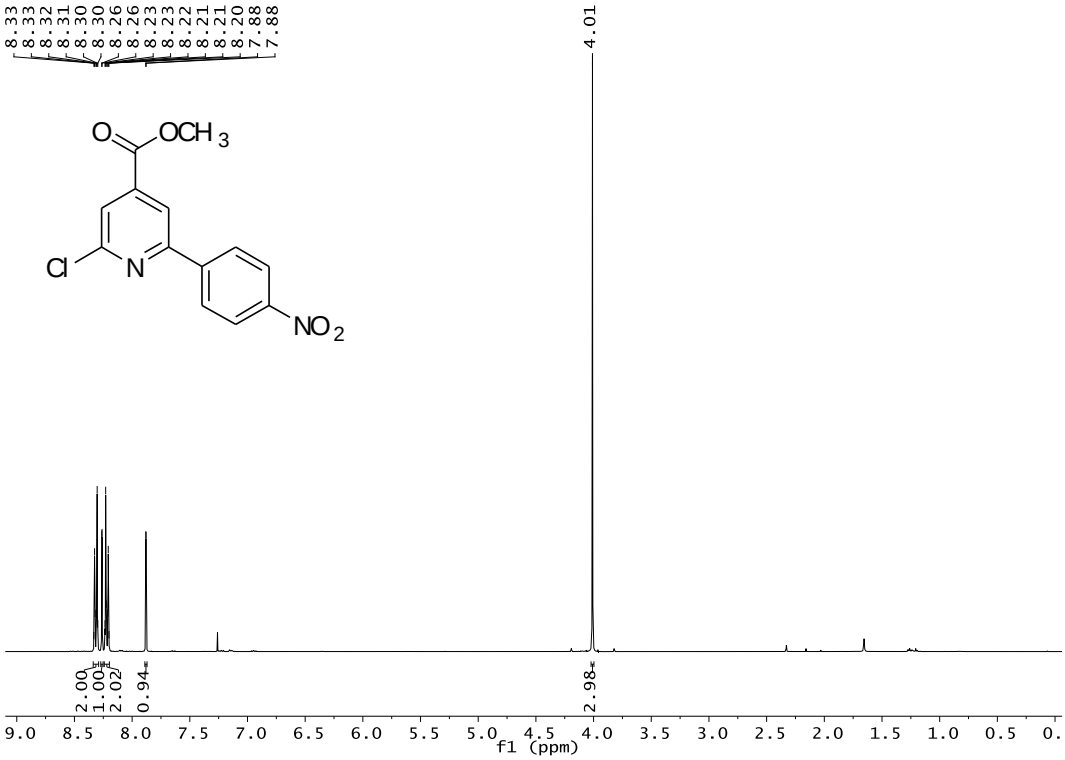
^{1}H NMR (700 MHz, $CDCl_3$) - 296



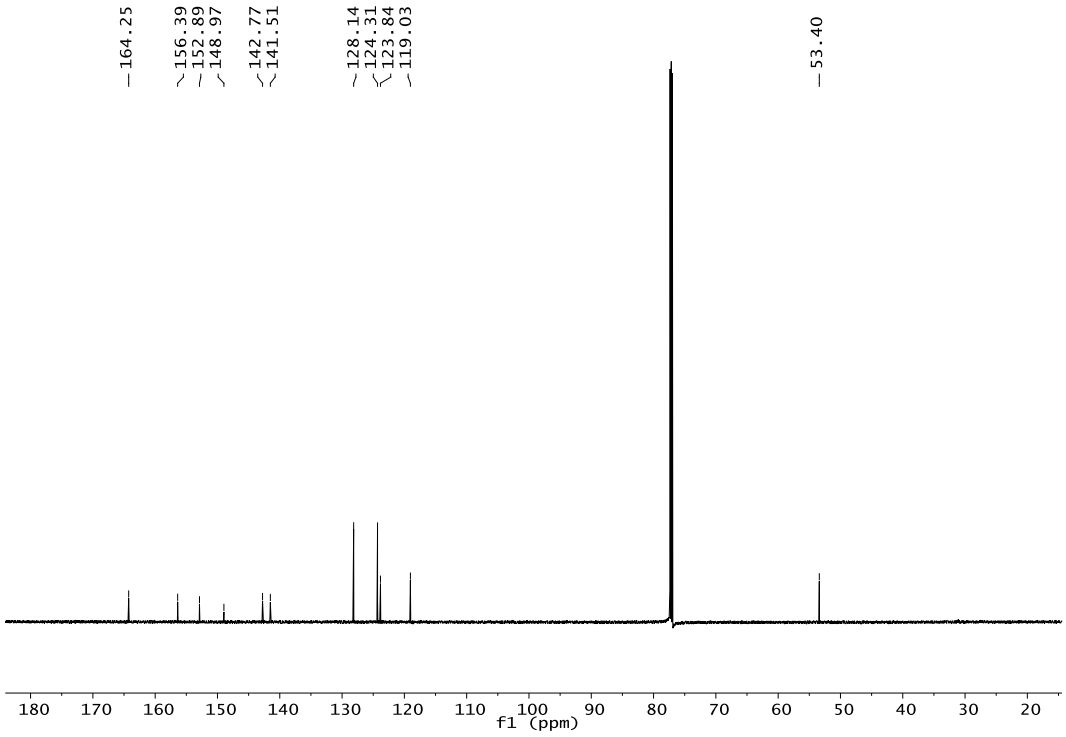
^{13}C NMR (176 MHz, $CDCl_3$) - 296



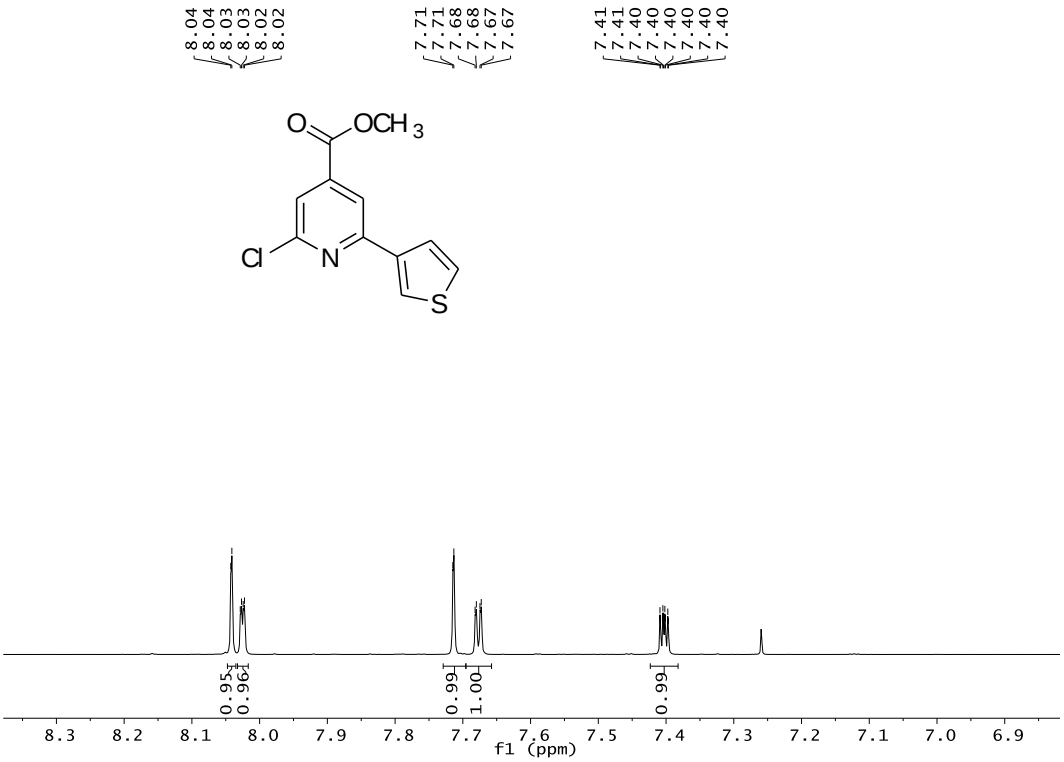
^{1}H NMR (700 MHz, $CDCl_3$) - 310



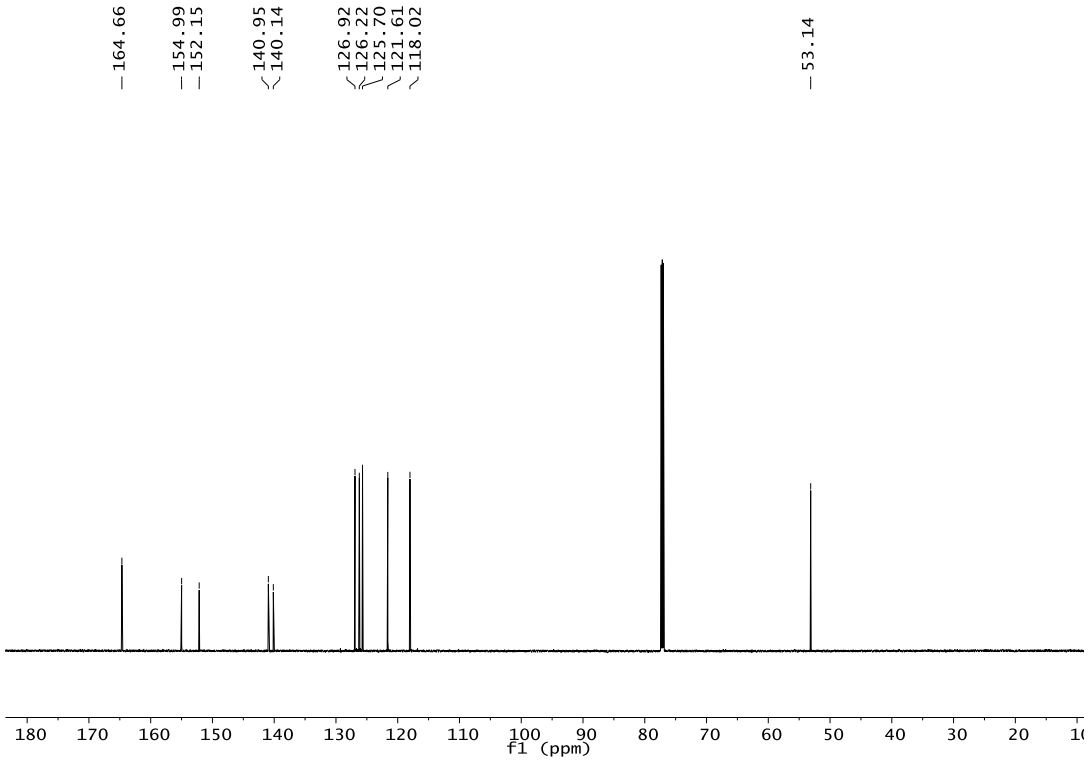
^{13}C NMR (176 MHz, $CDCl_3$) - 310



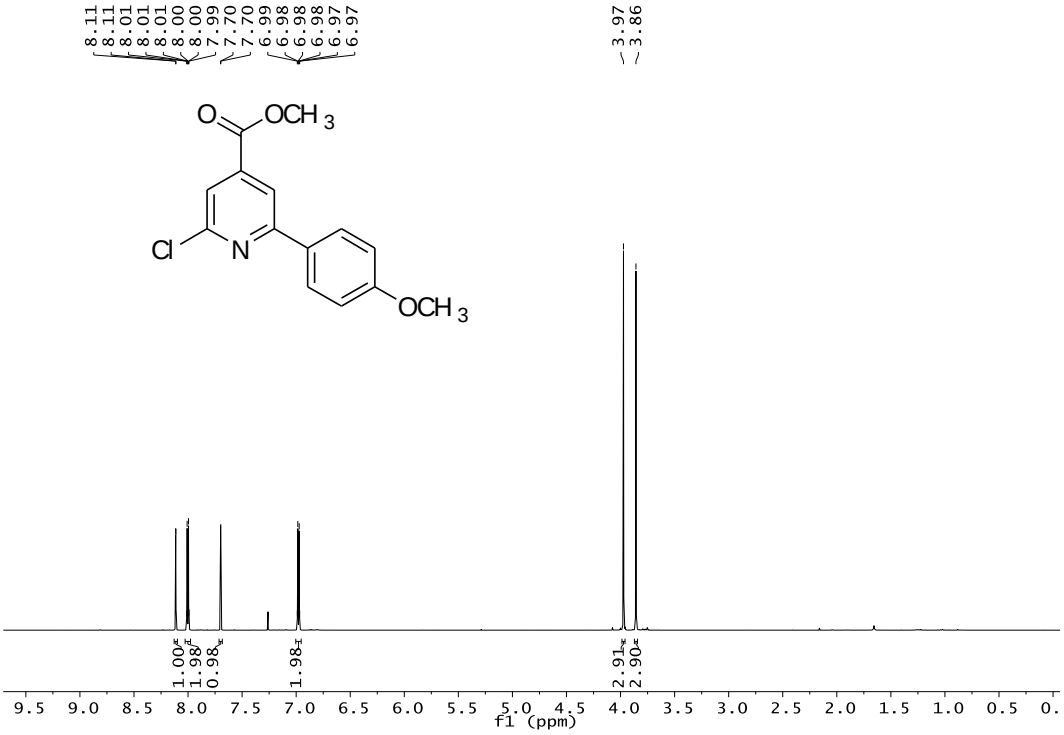
^{1}H NMR (700 MHz, $CDCl_3$) - 311



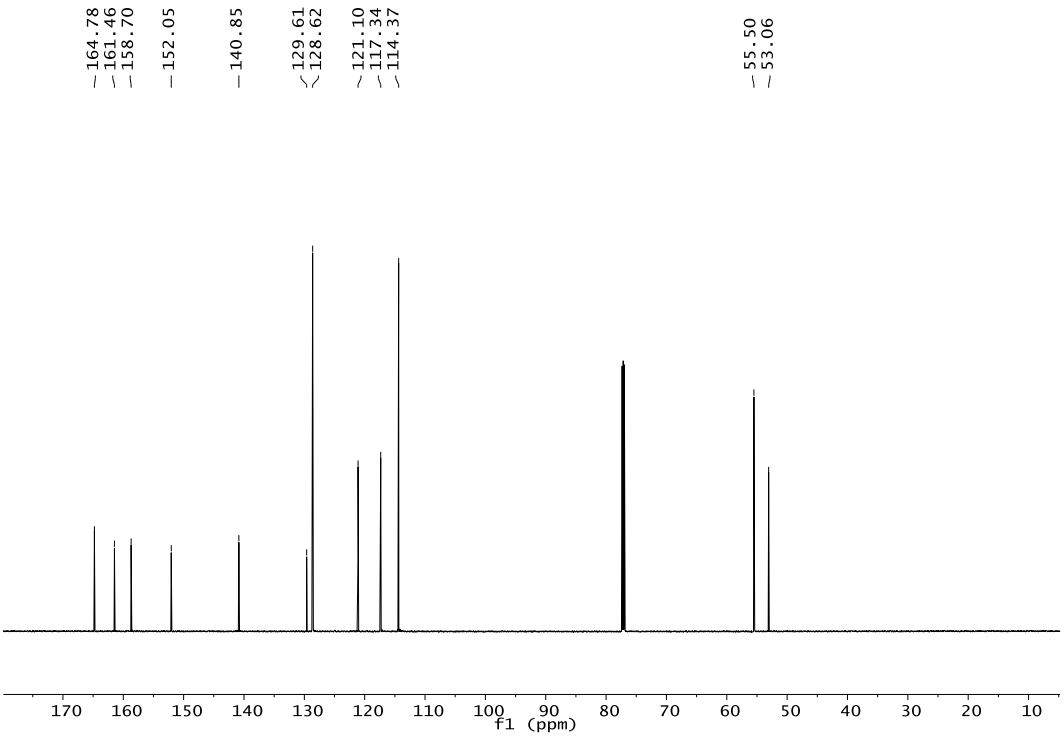
^{13}C NMR (176 MHz, $CDCl_3$) - 311



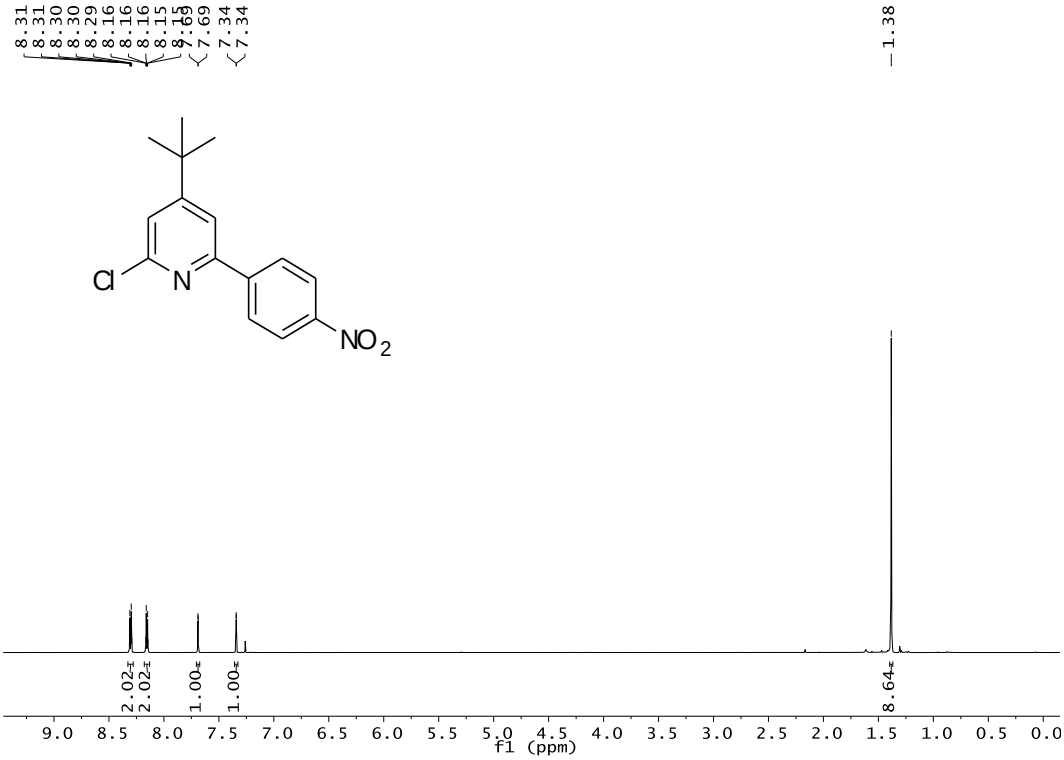
^{1}H NMR (700 MHz, $CDCl_3$) - 312



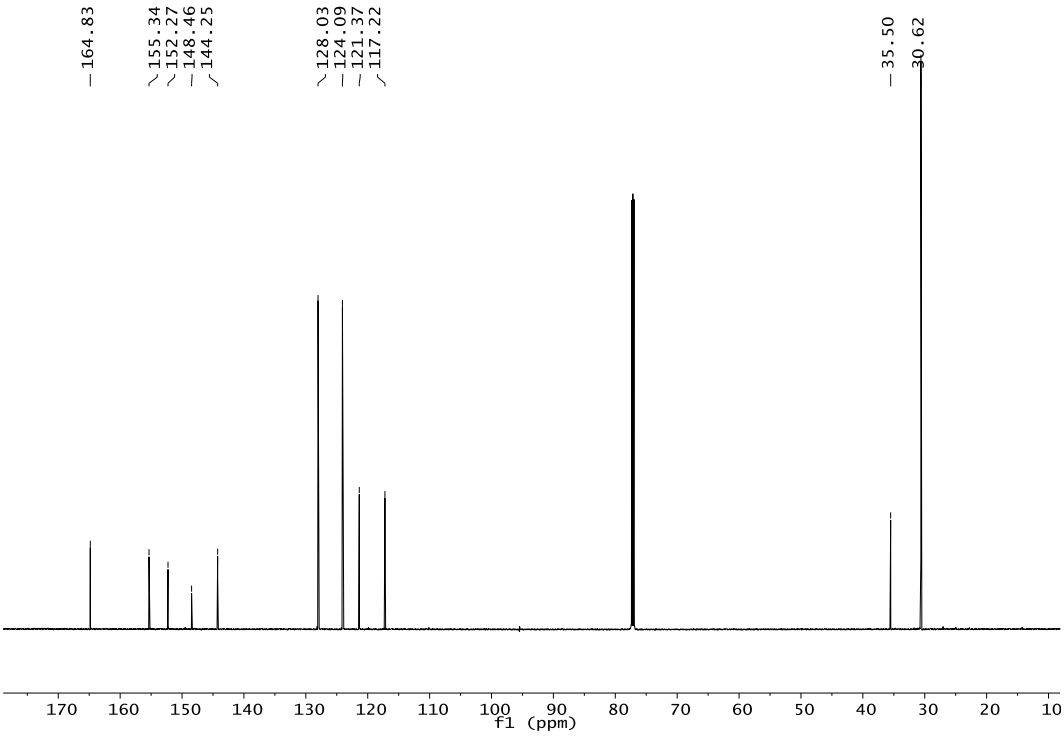
^{13}C NMR (176 MHz, $CDCl_3$) - 312



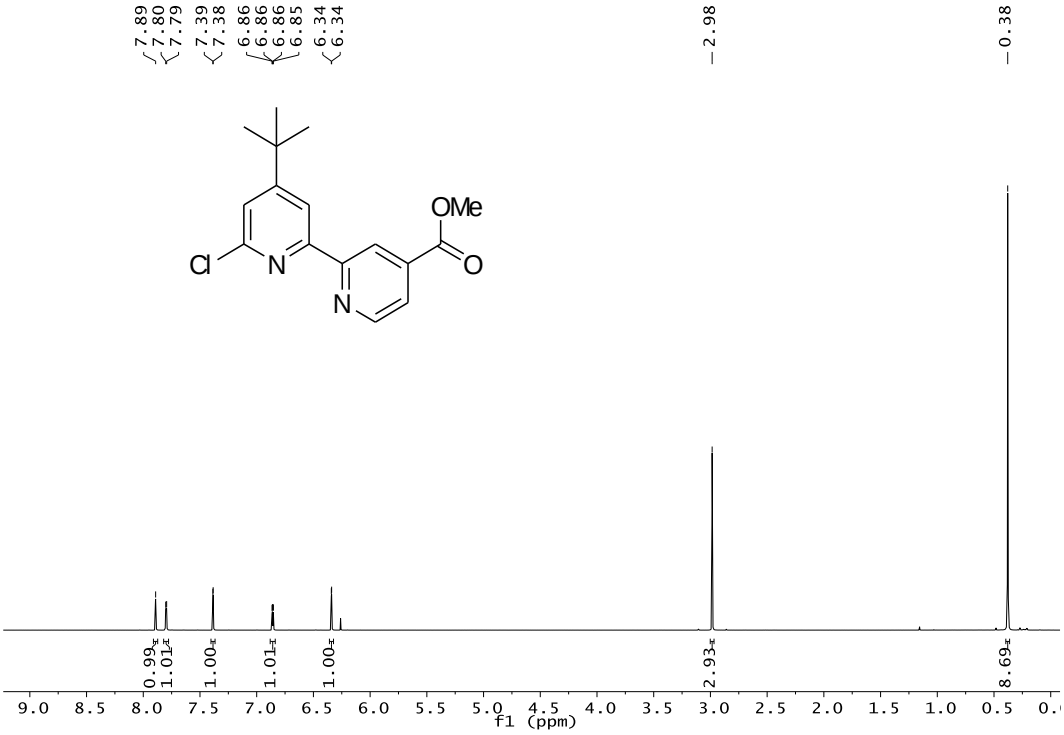
^{1}H NMR (700 MHz, $CDCl_3$) - 313



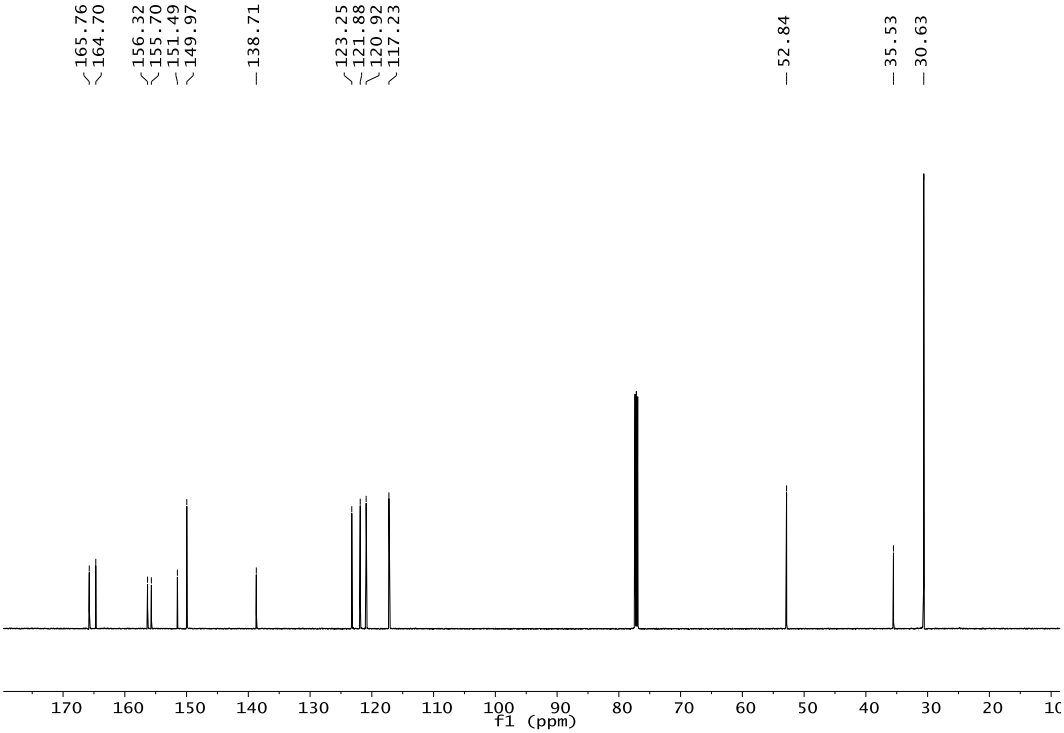
^{13}C NMR (176 MHz, $CDCl_3$) - 313



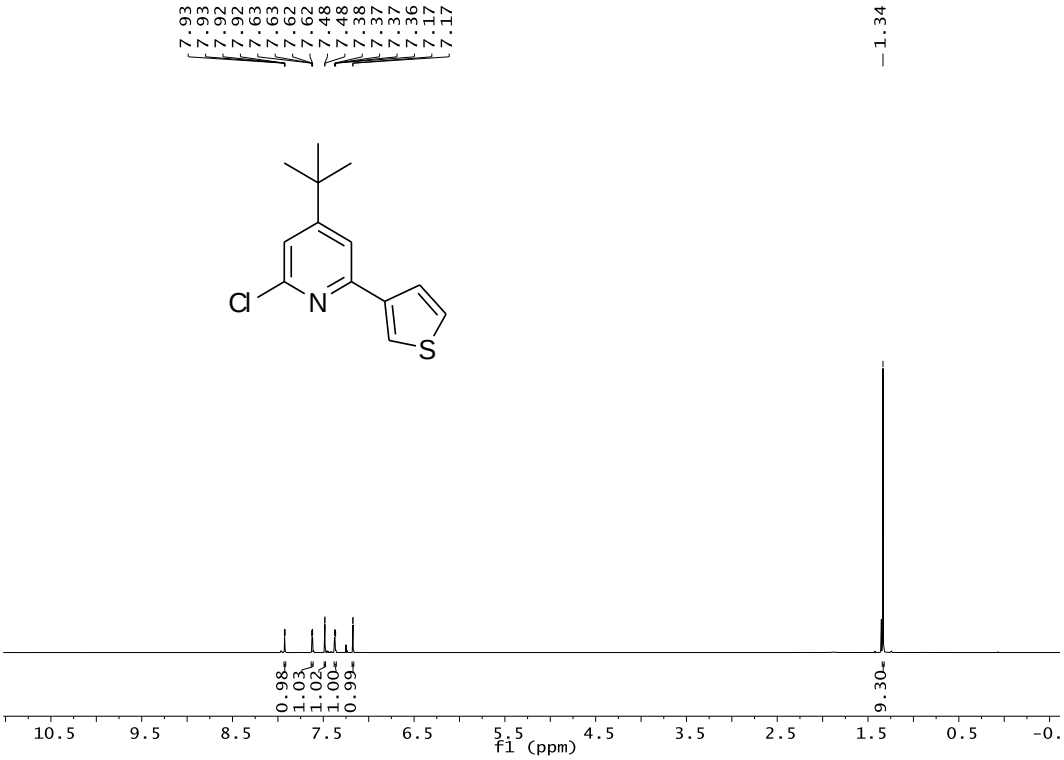
^{1}H NMR (600 MHz, $CDCl_3$) - 314



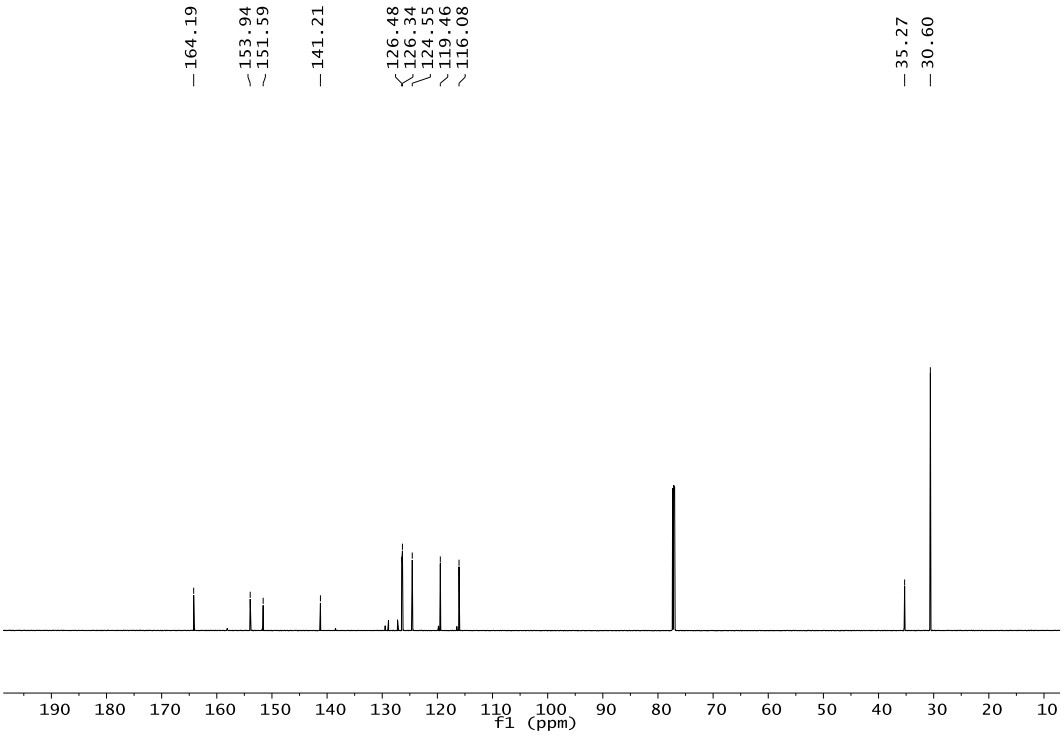
^{13}C NMR (151 MHz, $CDCl_3$) - 314



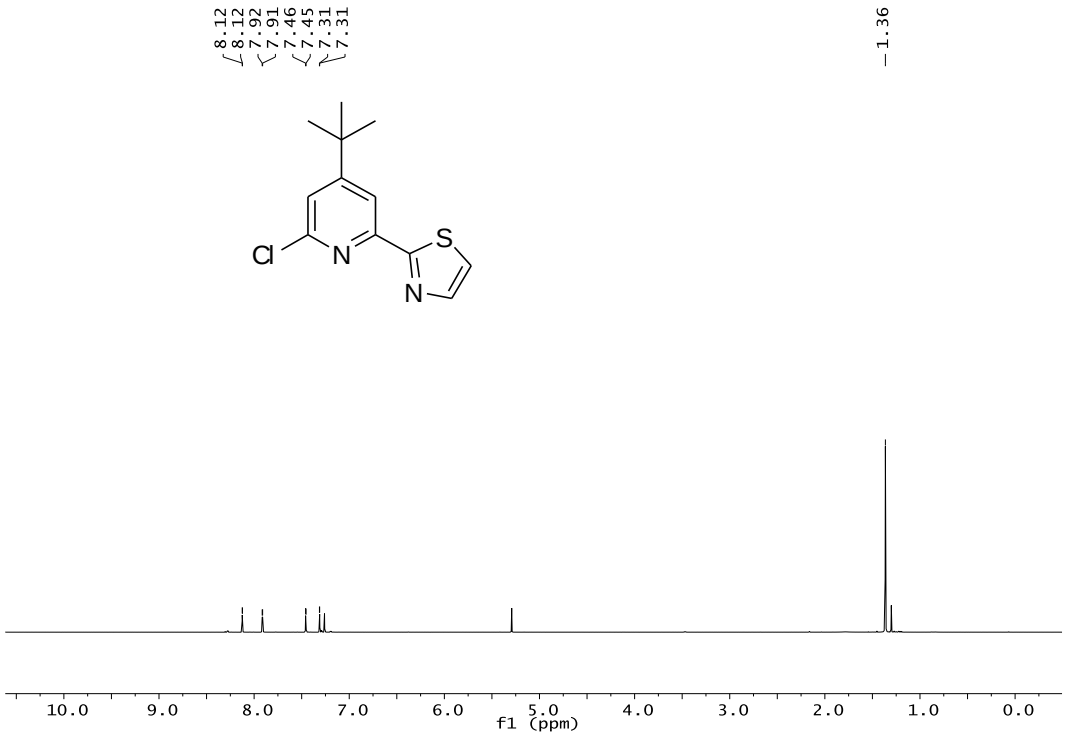
^{1}H NMR (700 MHz, $CDCl_3$) - 315



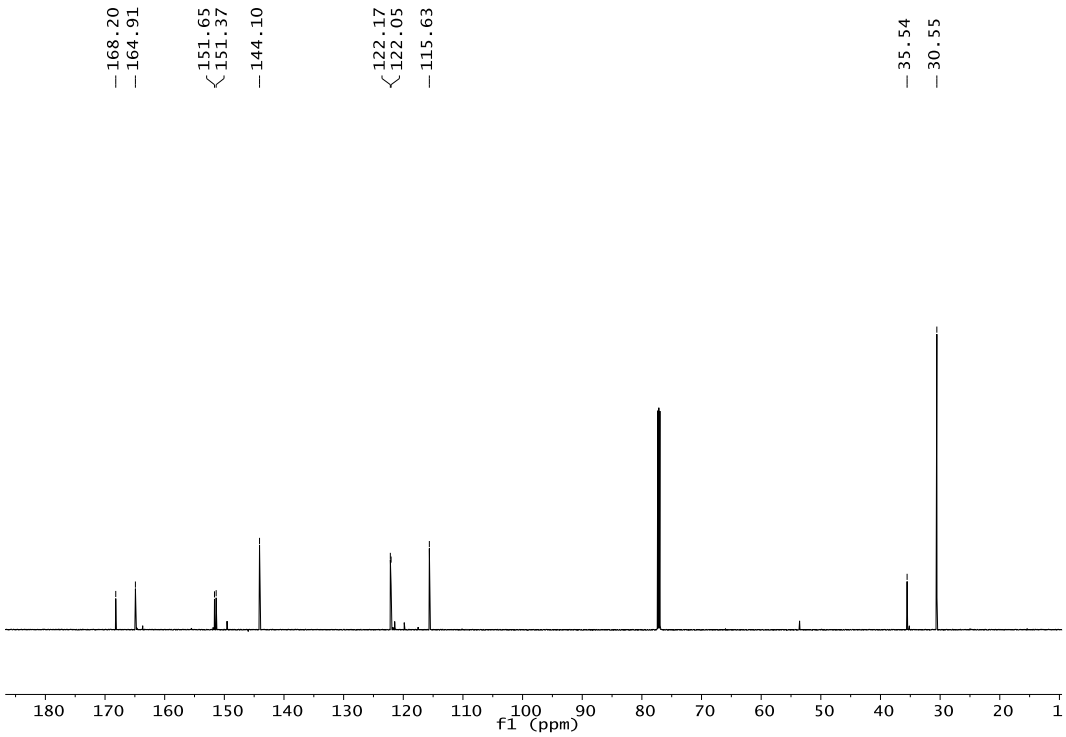
^{13}C NMR (176 MHz, $CDCl_3$) - 315



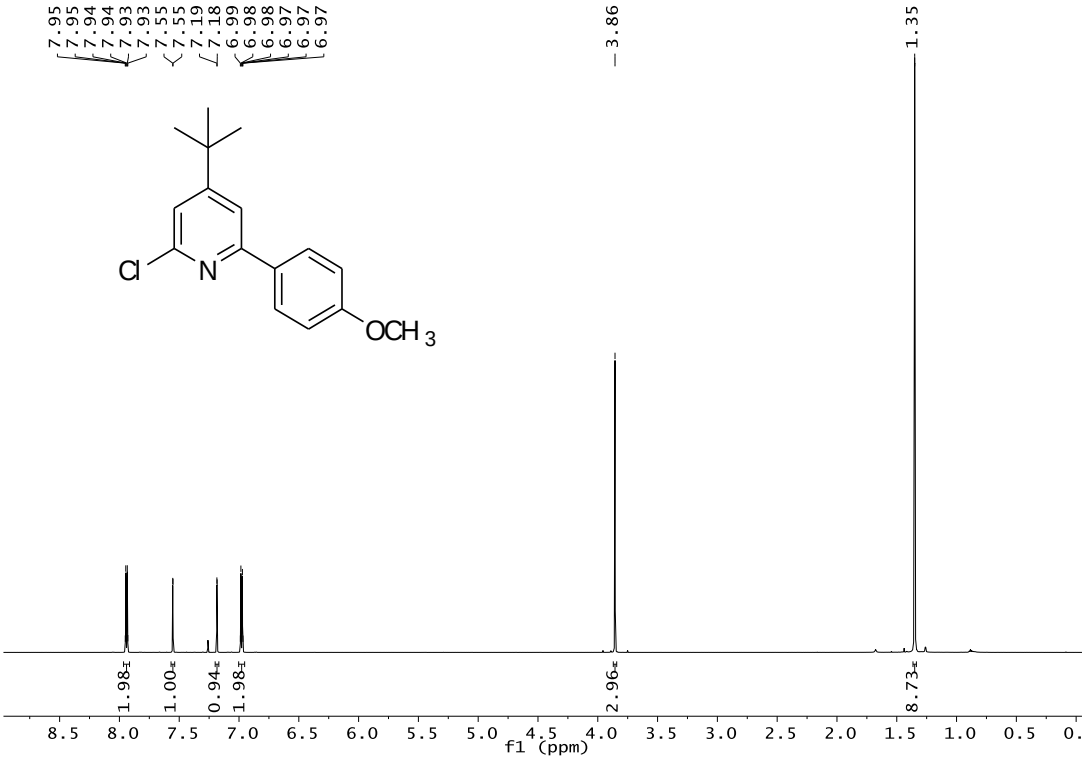
^{1}H NMR (700 MHz, $CDCl_3$) - 316



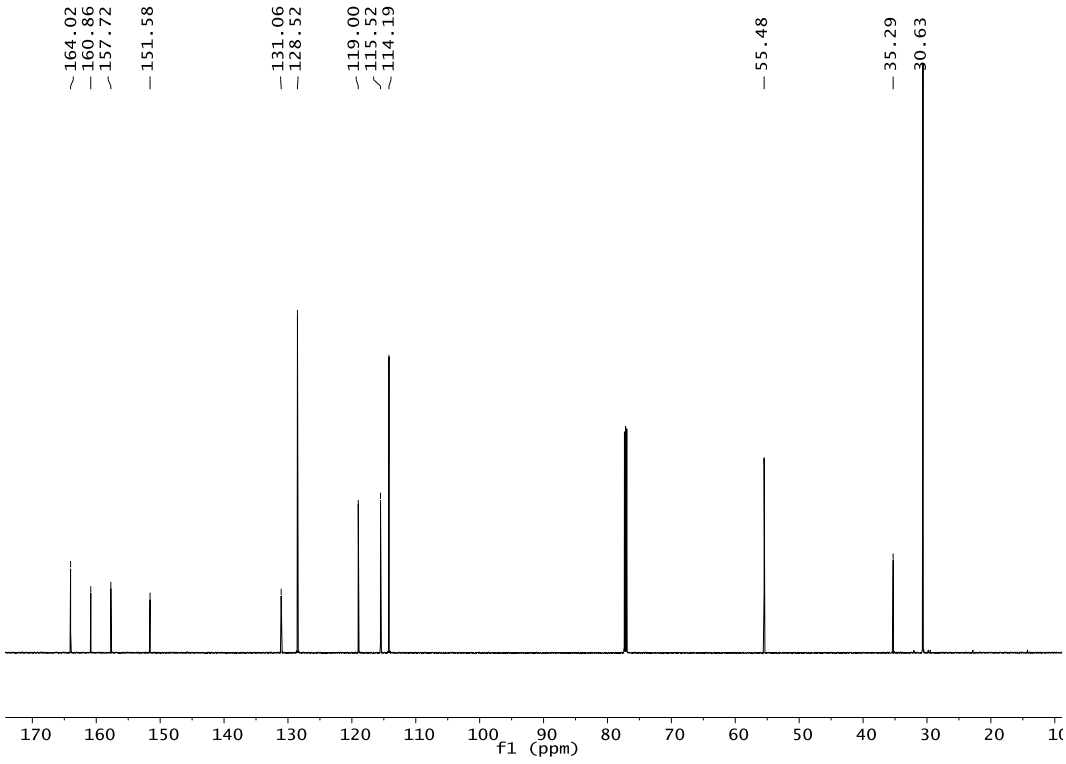
^{13}C NMR (176 MHz, $CDCl_3$) - 316



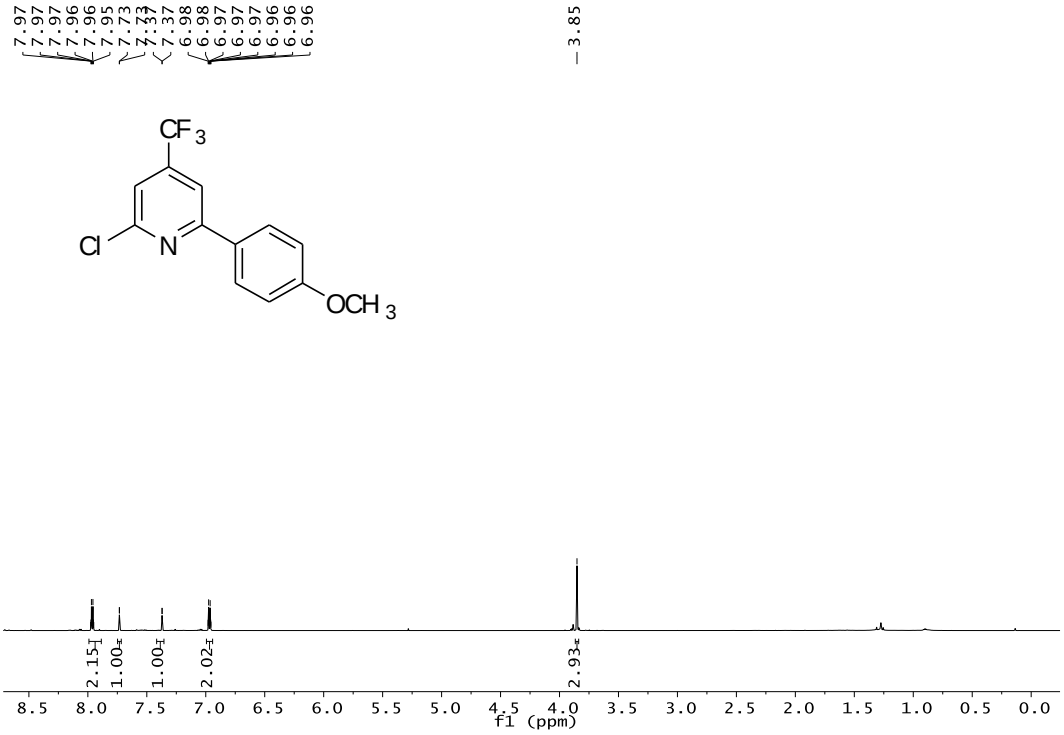
^{1}H NMR (700 MHz, $CDCl_3$) - 317



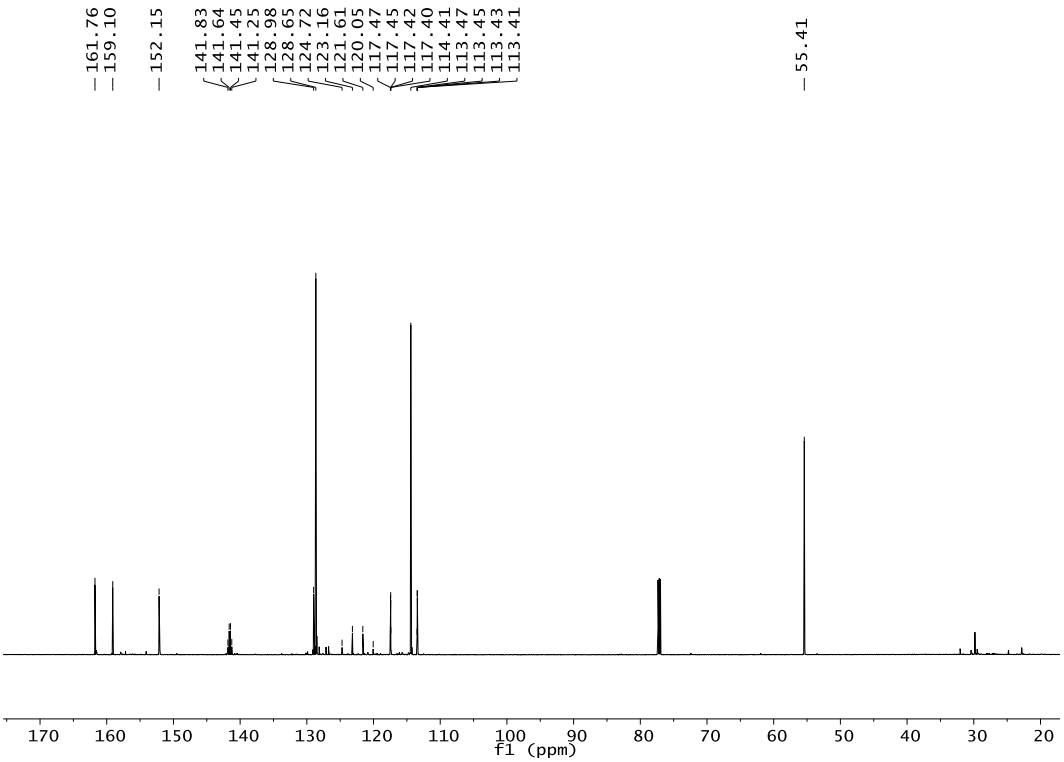
^{13}C NMR (176 MHz, $CDCl_3$) - 317



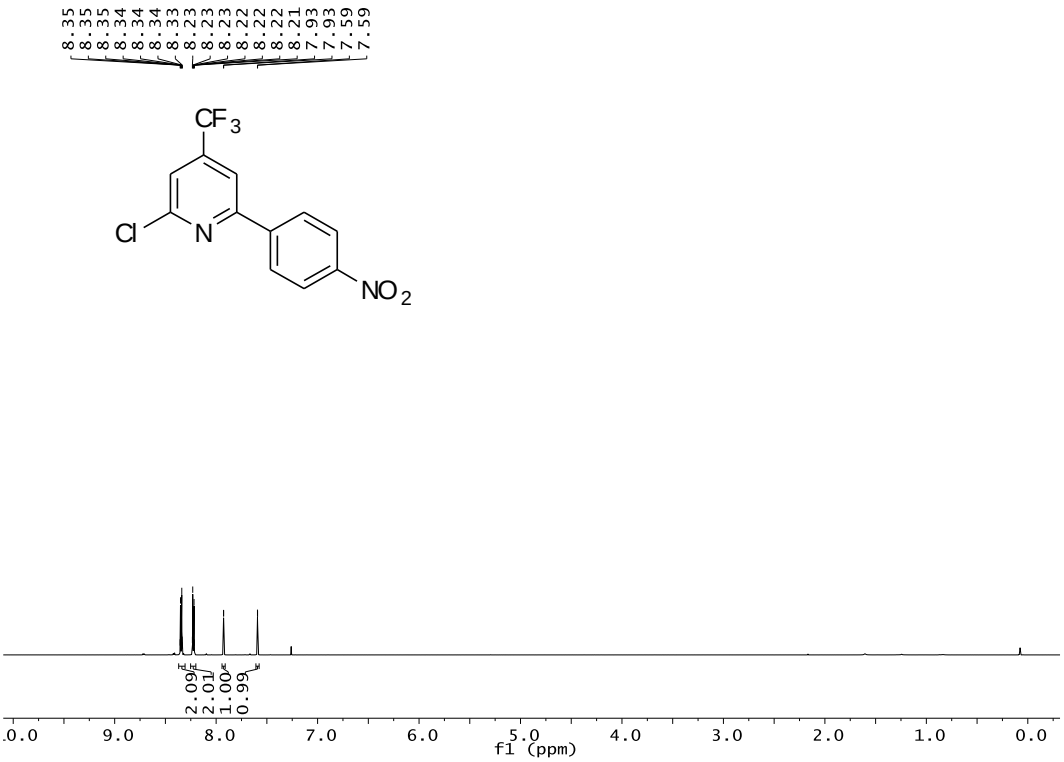
^{1}H NMR (700 MHz, $CDCl_3$) - 318



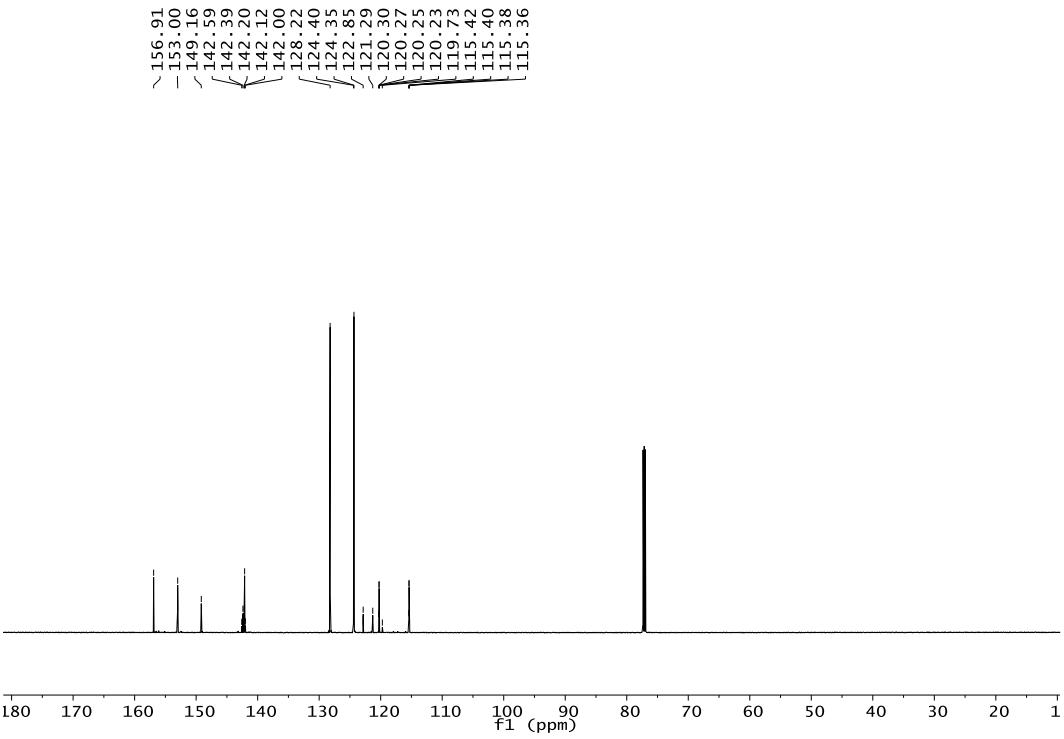
^{13}C NMR (176 MHz, $CDCl_3$) - 318



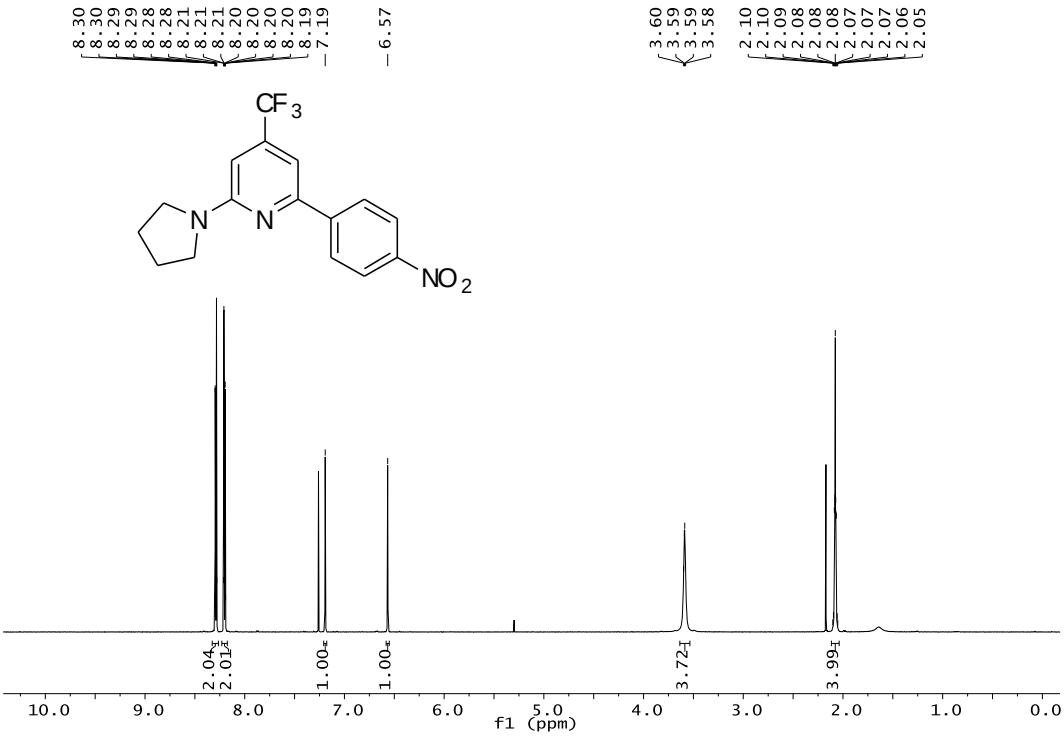
^{1}H NMR (700 MHz, $CDCl_3$) - 319



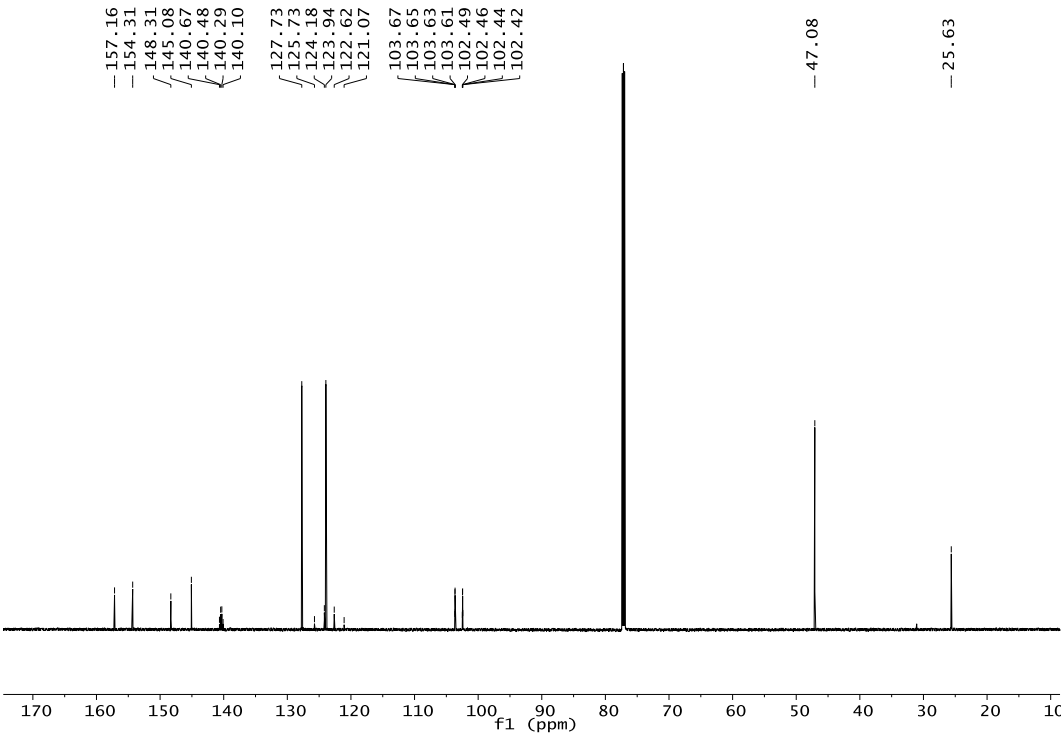
^{13}C NMR (176 MHz, $CDCl_3$) - 319



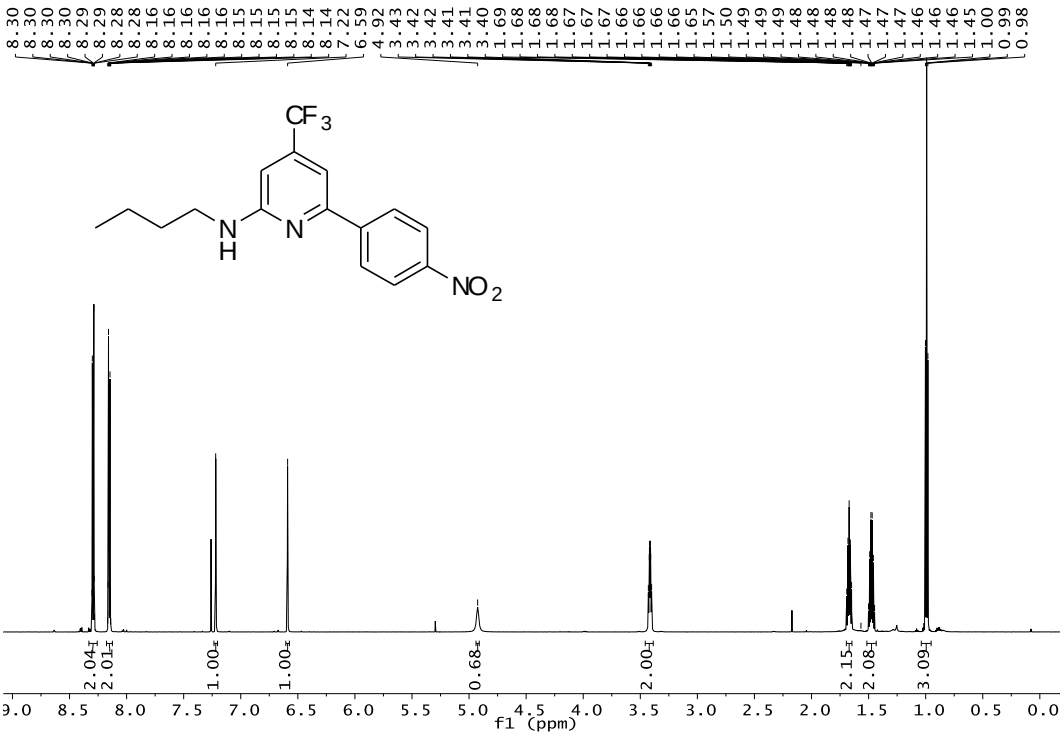
^{1}H NMR (700 MHz, $CDCl_3$) - 320



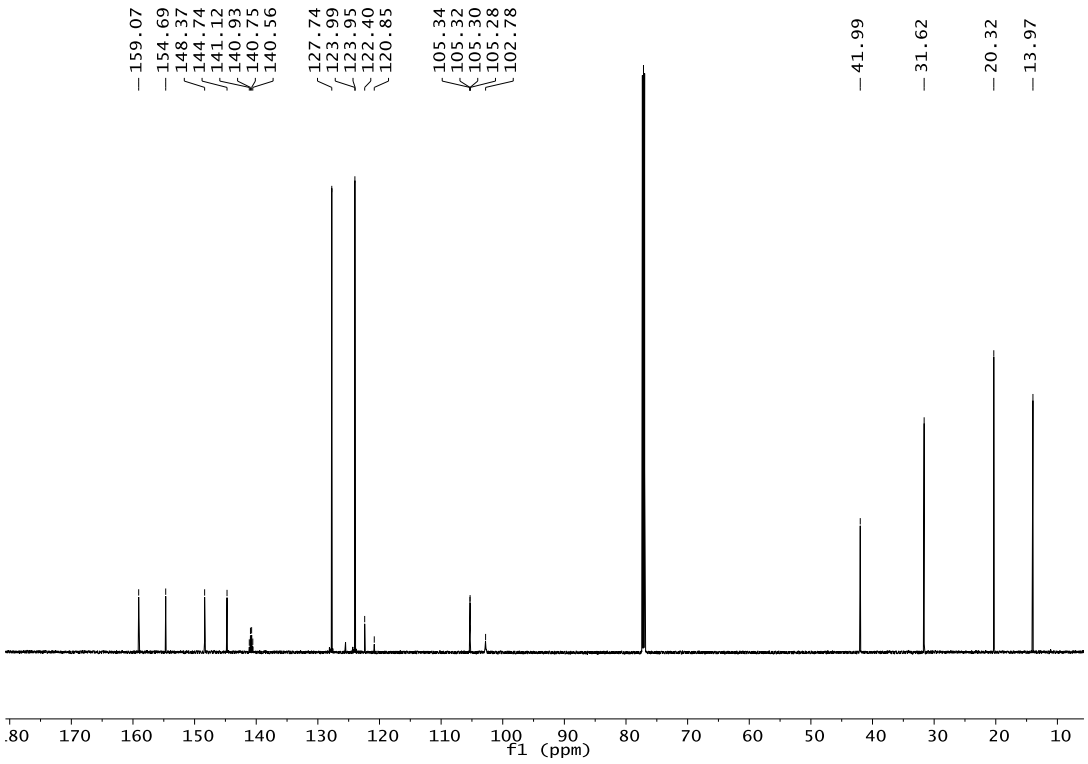
^{13}C NMR (176 MHz, $CDCl_3$) - 320



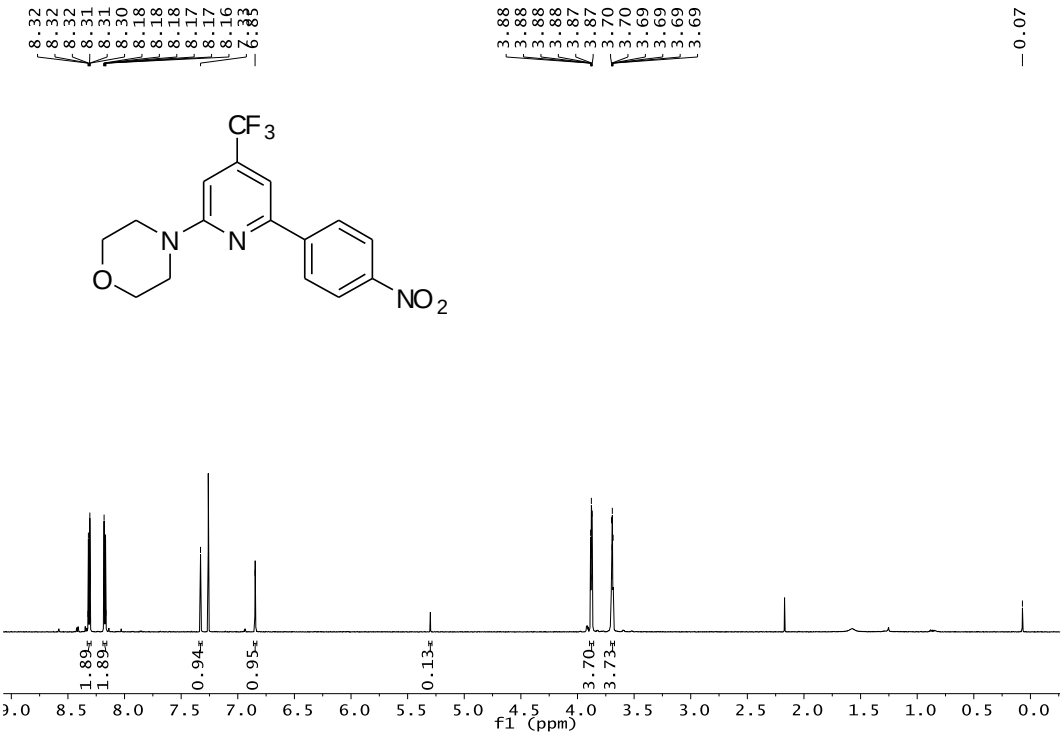
^{1}H NMR (700 MHz, $CDCl_3$) - 321



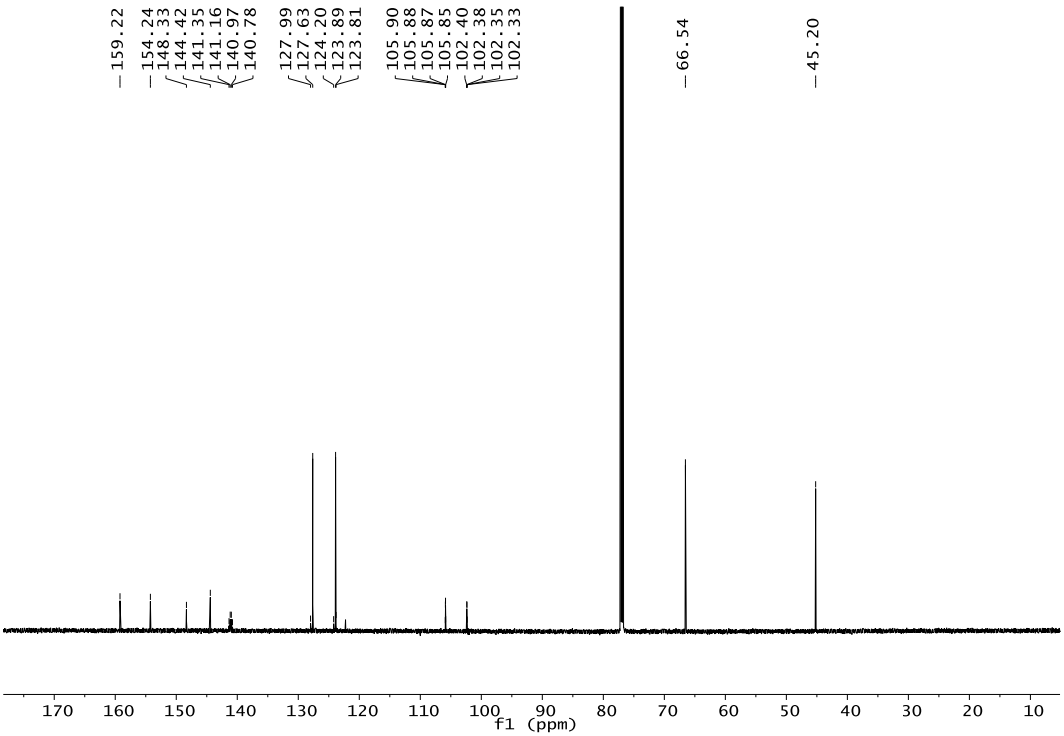
^{13}C NMR (176 MHz, $CDCl_3$) - 321



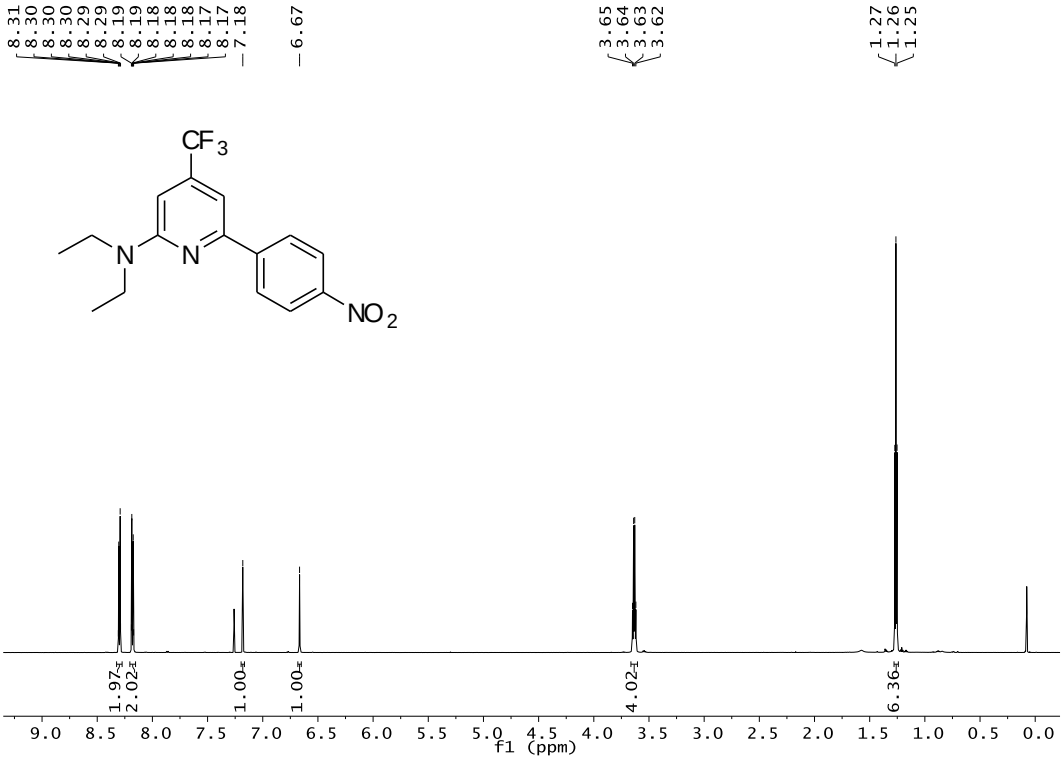
^{1}H NMR (700 MHz, $CDCl_3$) - 322



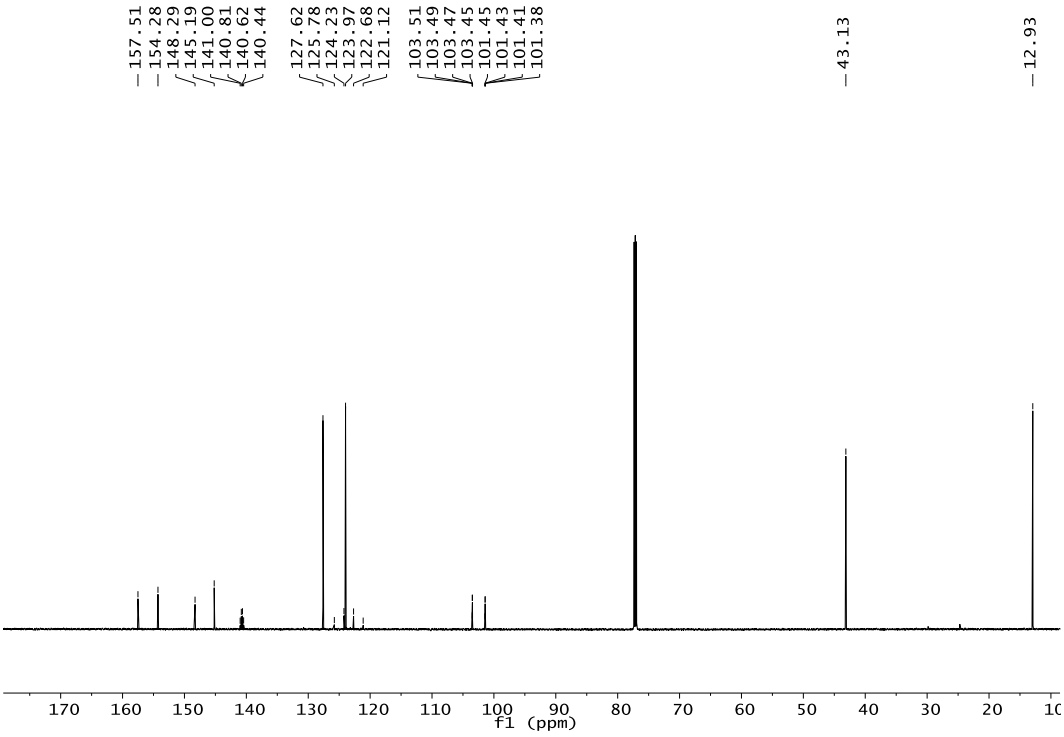
^{13}C NMR (176 MHz, $CDCl_3$) - 322



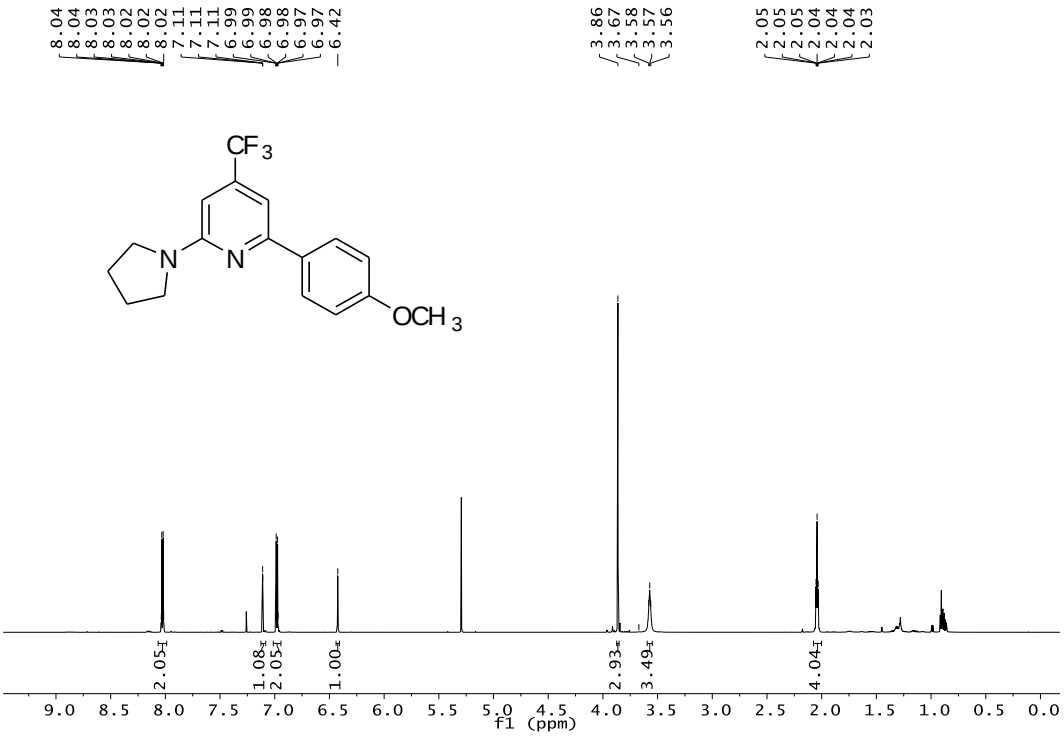
^{1}H NMR (700 MHz, $CDCl_3$) - 323



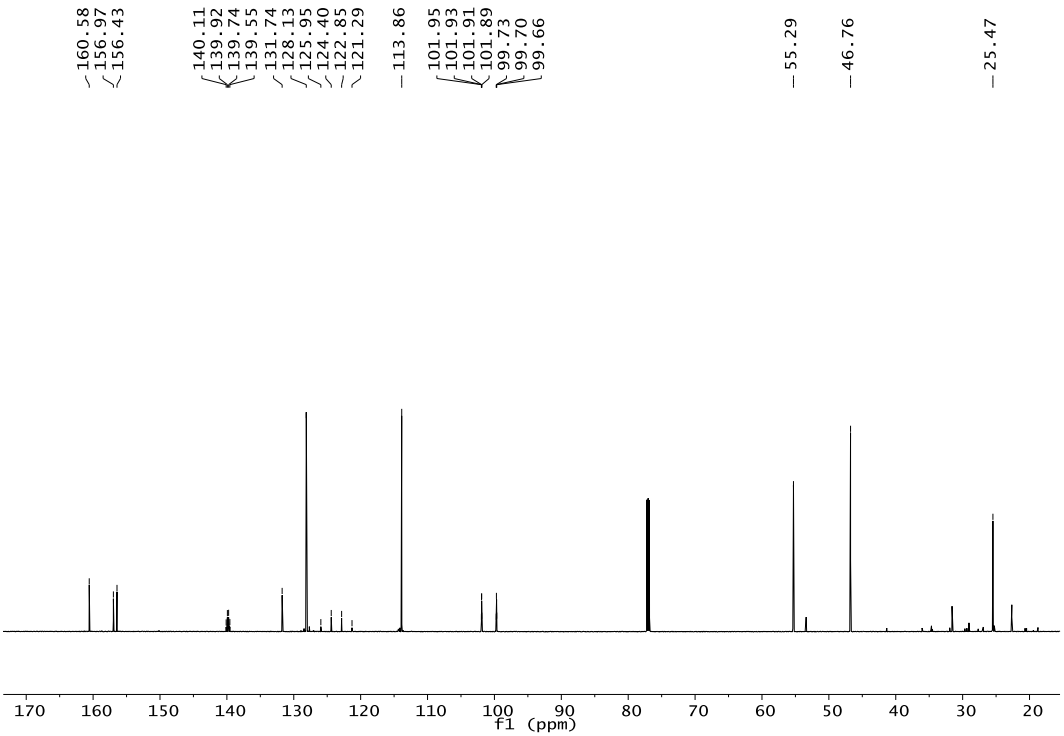
^{13}C NMR (176 MHz, $CDCl_3$) - 323



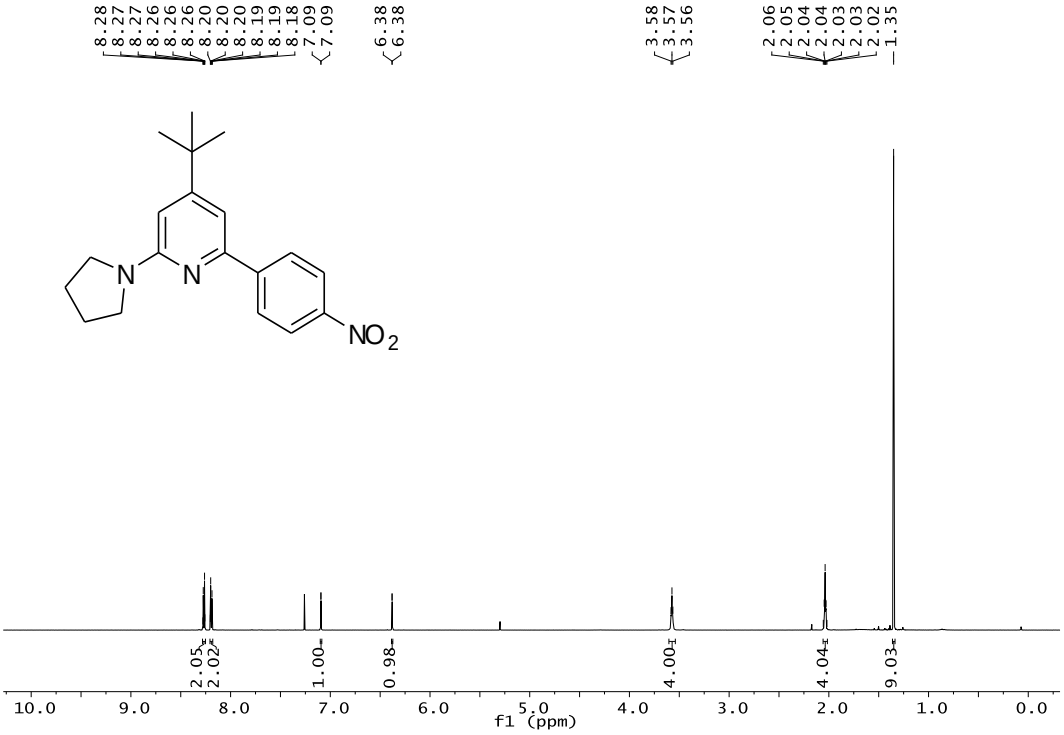
^{1}H NMR (700 MHz, $CDCl_3$) - 324



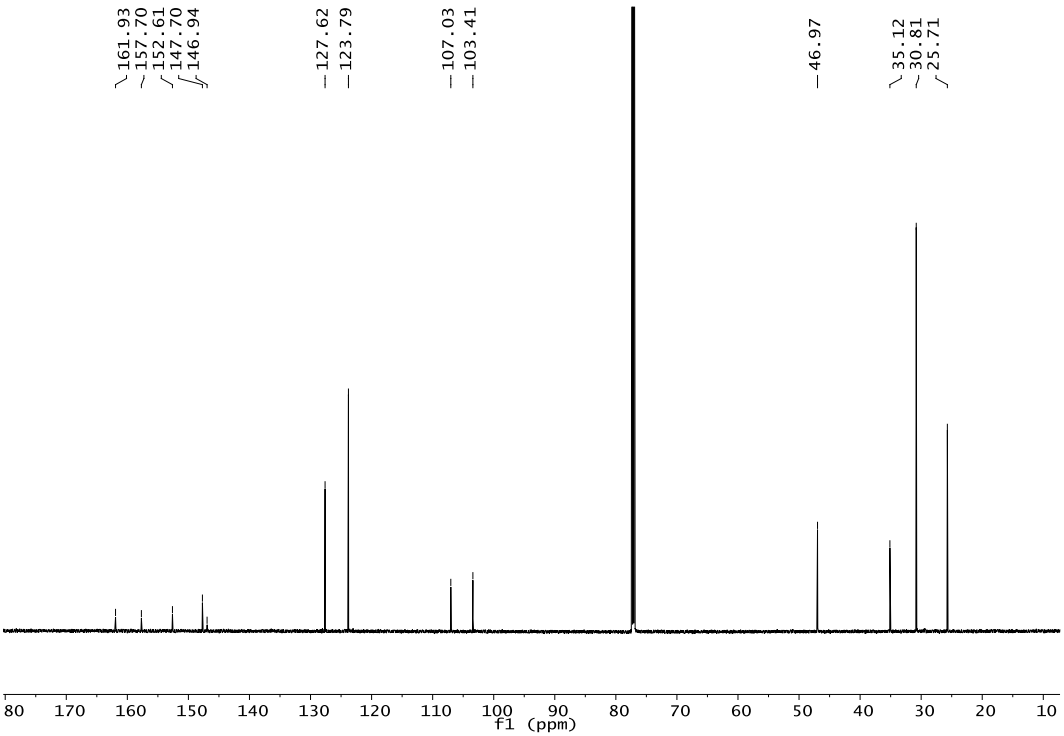
^{13}C NMR (176 MHz, $CDCl_3$) - 324



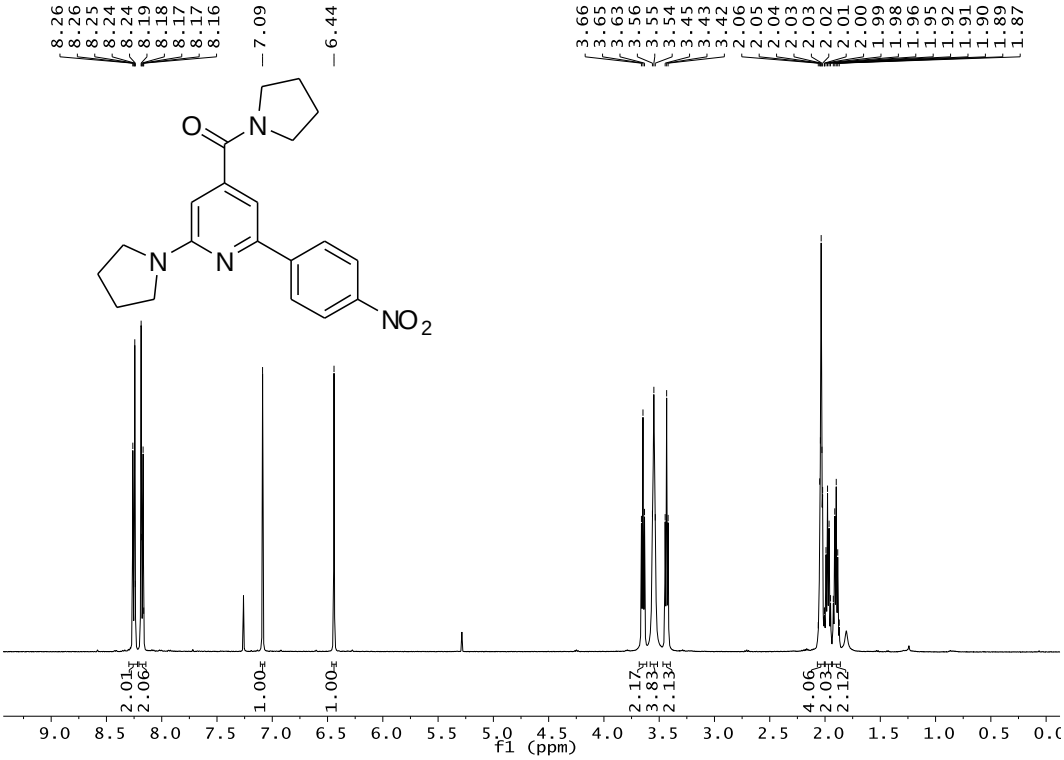
^{1}H NMR (700 MHz, $CDCl_3$) - 325



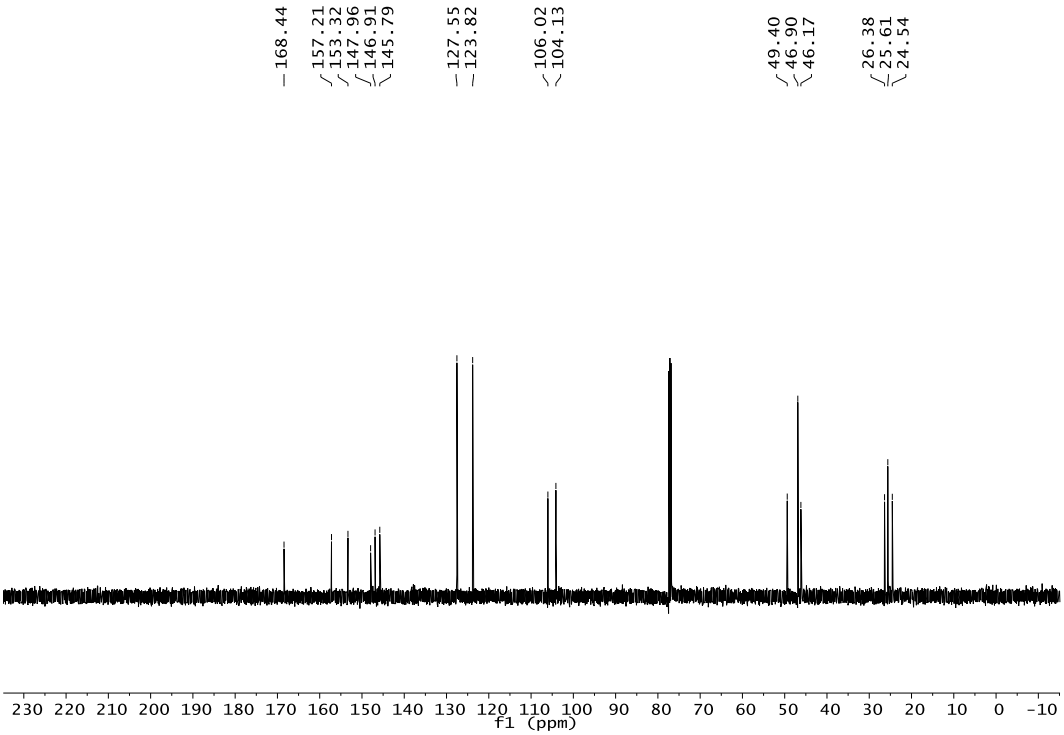
^{13}C NMR (176 MHz, $CDCl_3$) - 325



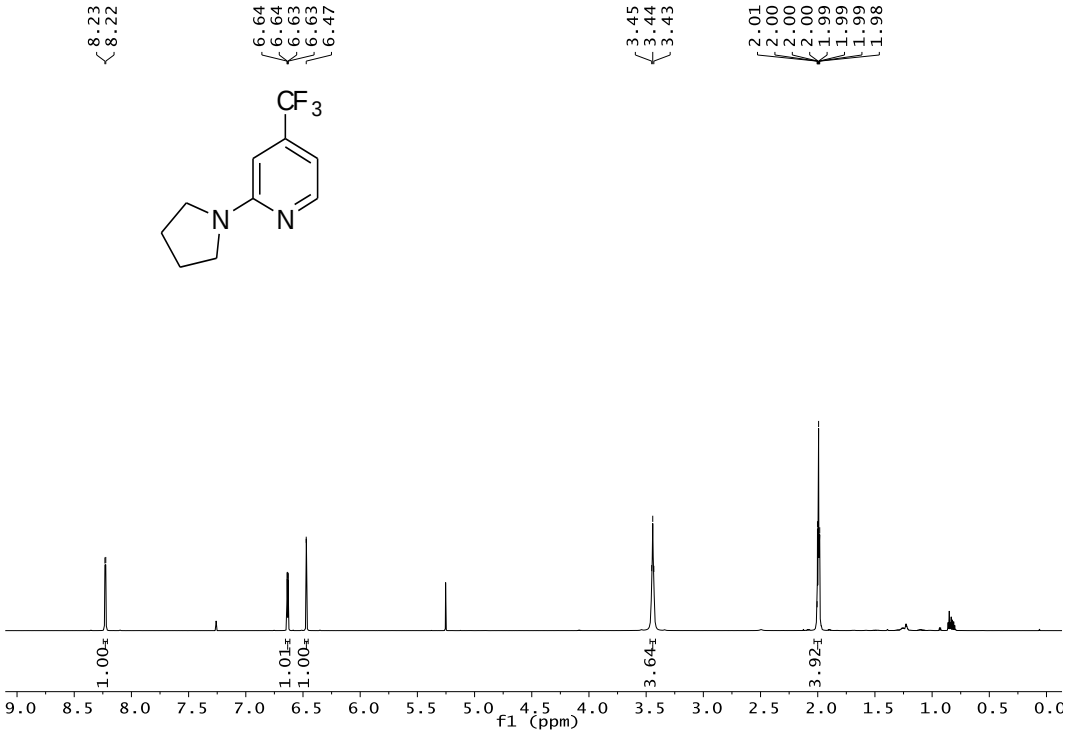
^{1}H NMR (500 MHz, $CDCl_3$) - 327



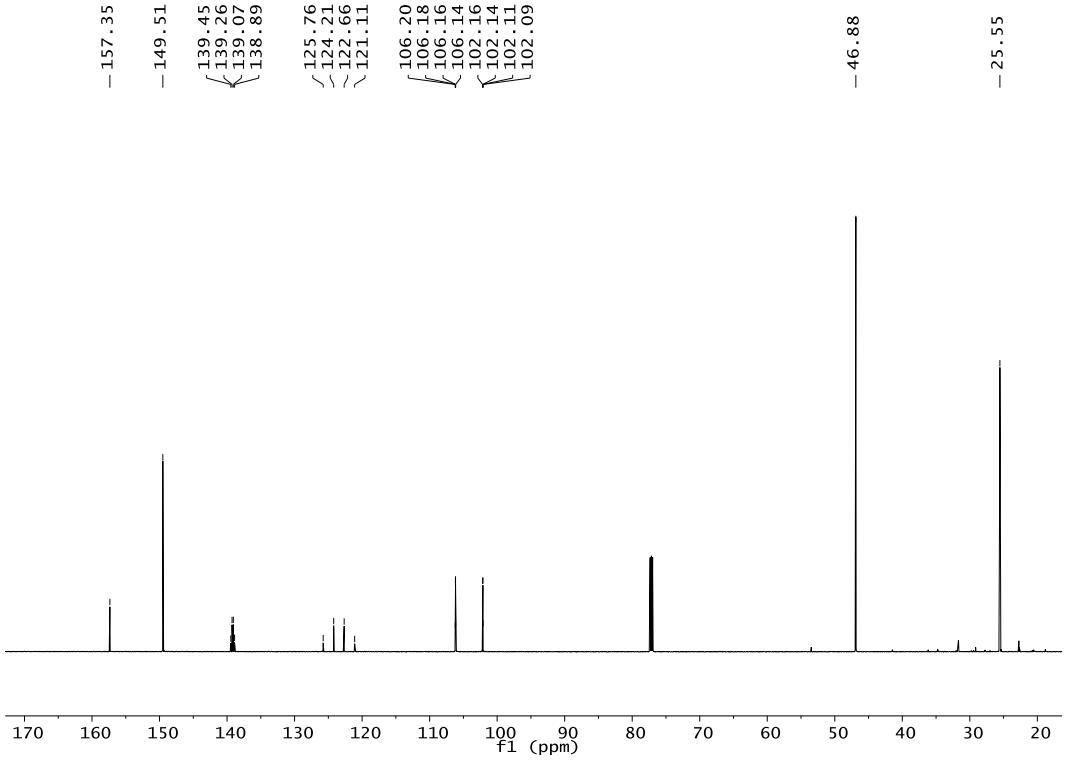
^{13}C NMR (125 MHz, $CDCl_3$) - 327



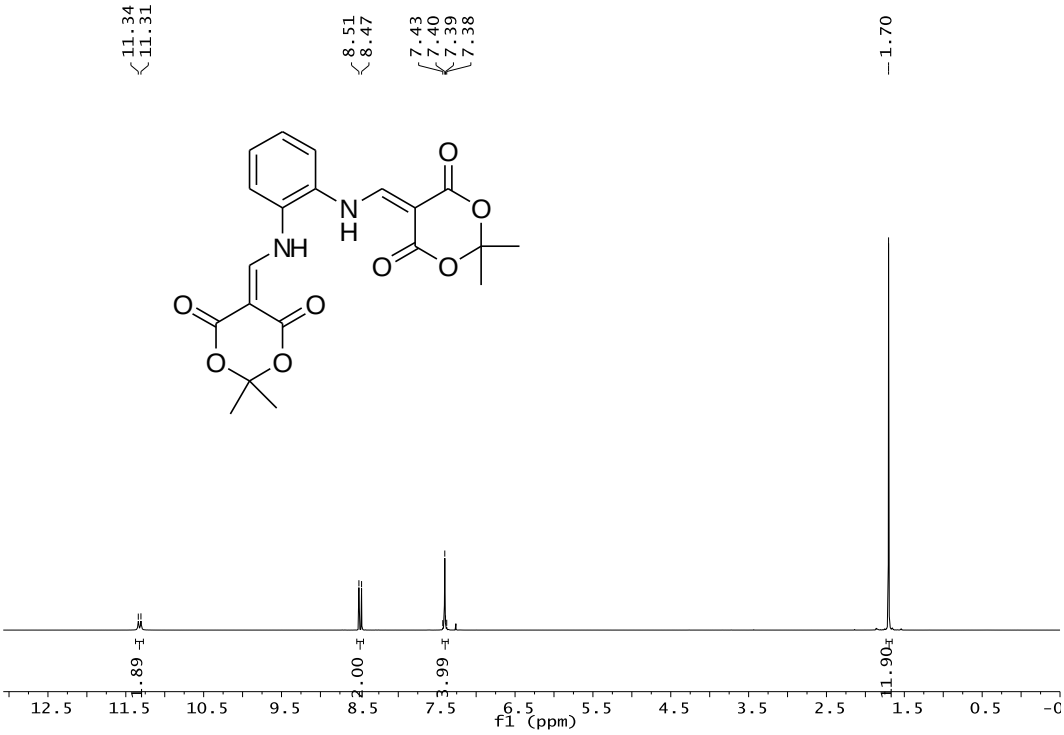
^{1}H NMR (700 MHz, $CDCl_3$) - 328



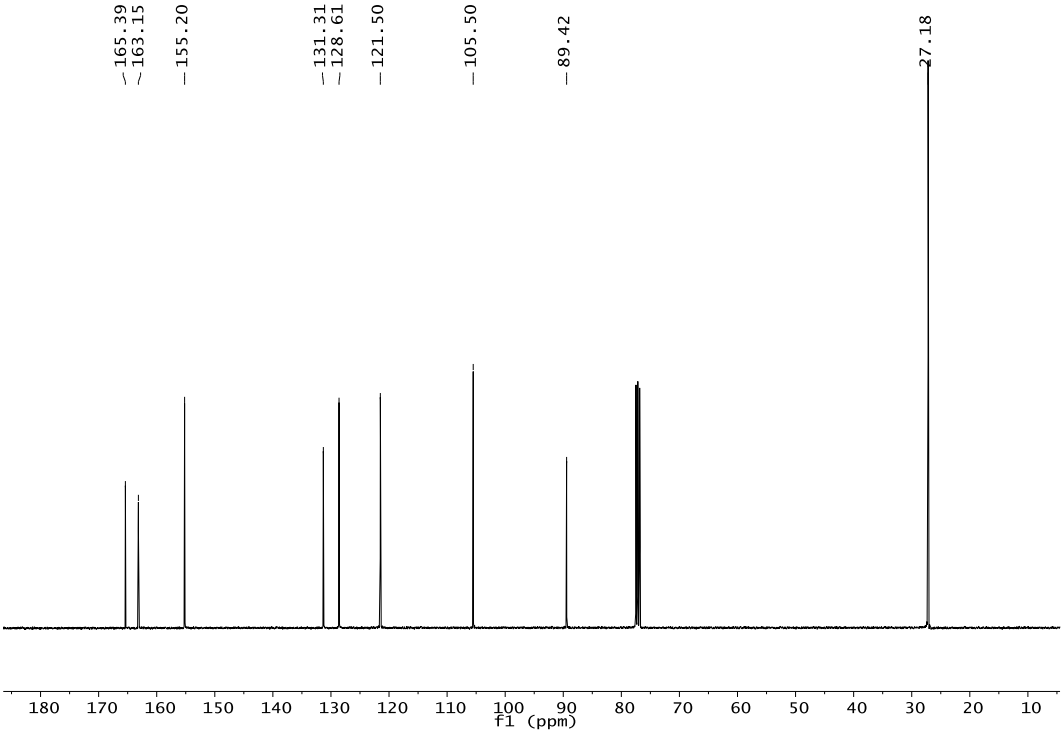
^{13}C NMR (176 MHz, $CDCl_3$) - 328



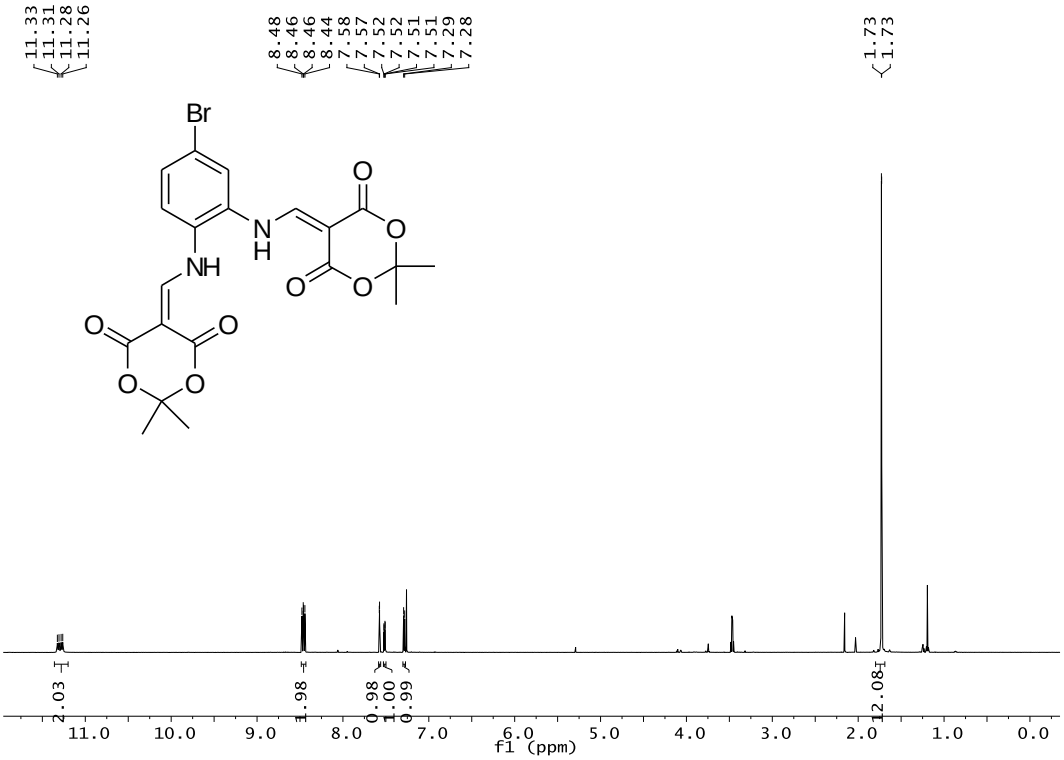
^{1}H NMR (700 MHz, $CDCl_3$) - 337



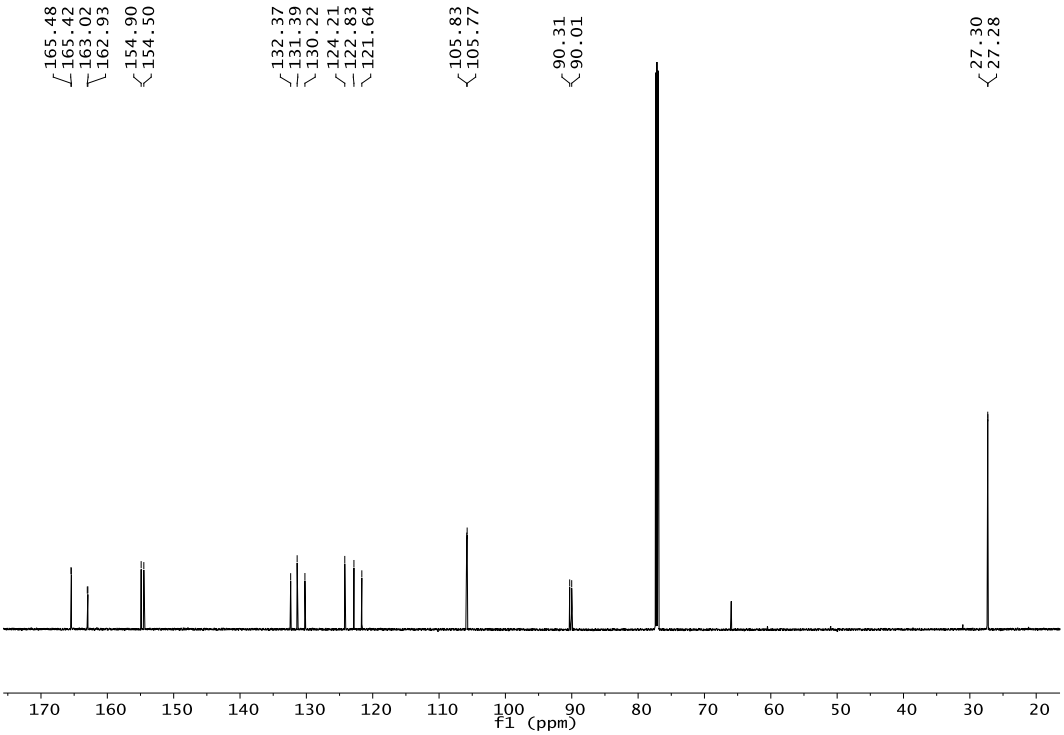
^{13}C NMR (176 MHz, $CDCl_3$) - 337



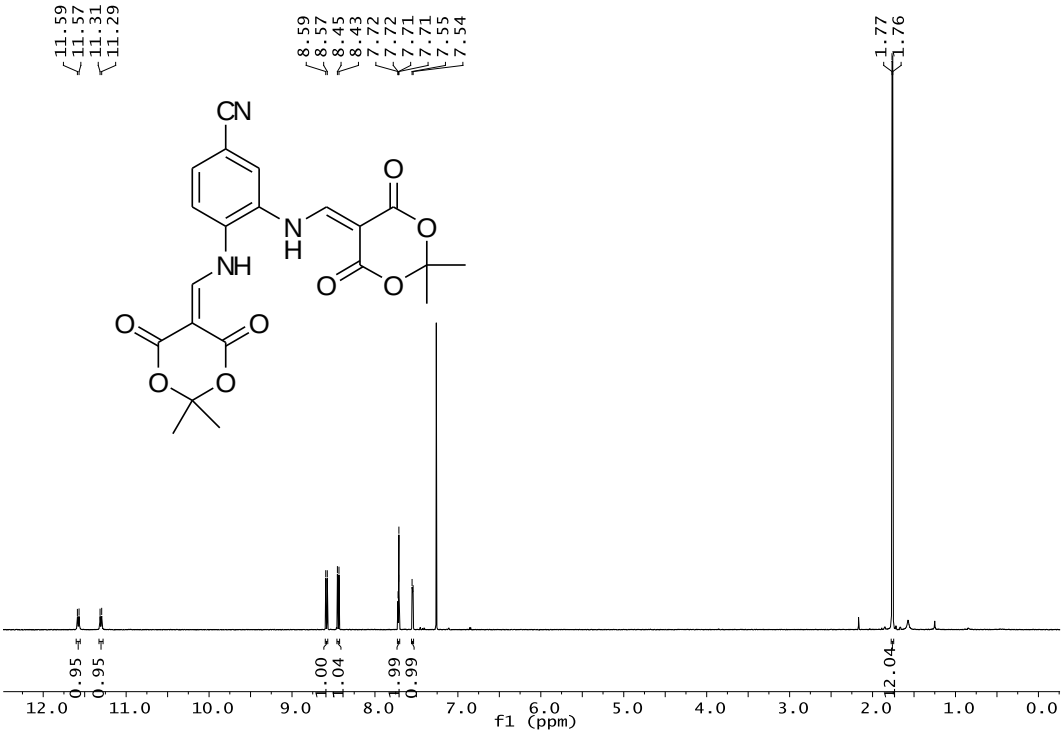
^{1}H NMR (700 MHz, $CDCl_3$) - 340



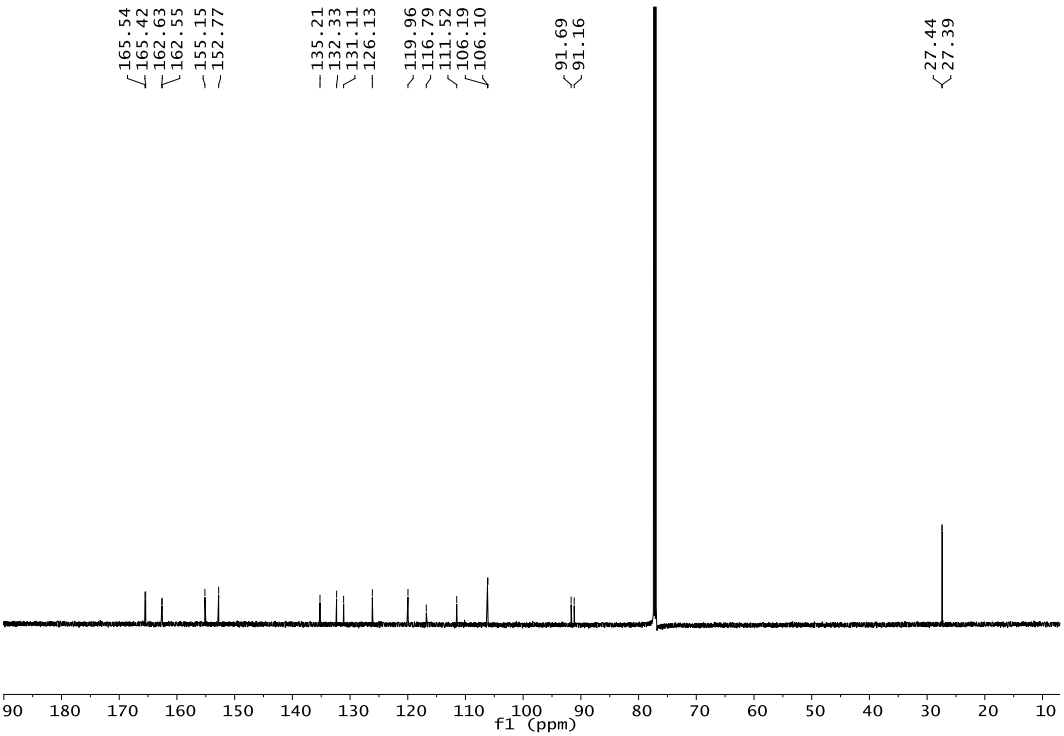
^{13}C NMR (176 MHz, $CDCl_3$) - 340



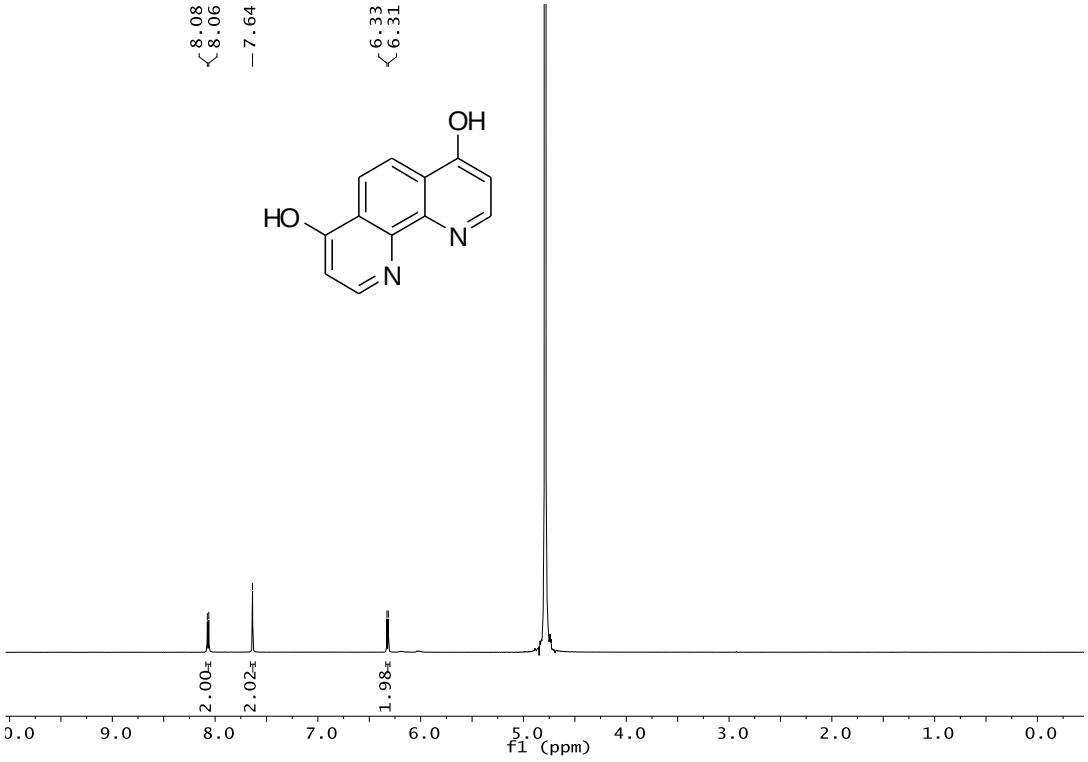
^{1}H NMR (700 MHz, $CDCl_3$) - 341



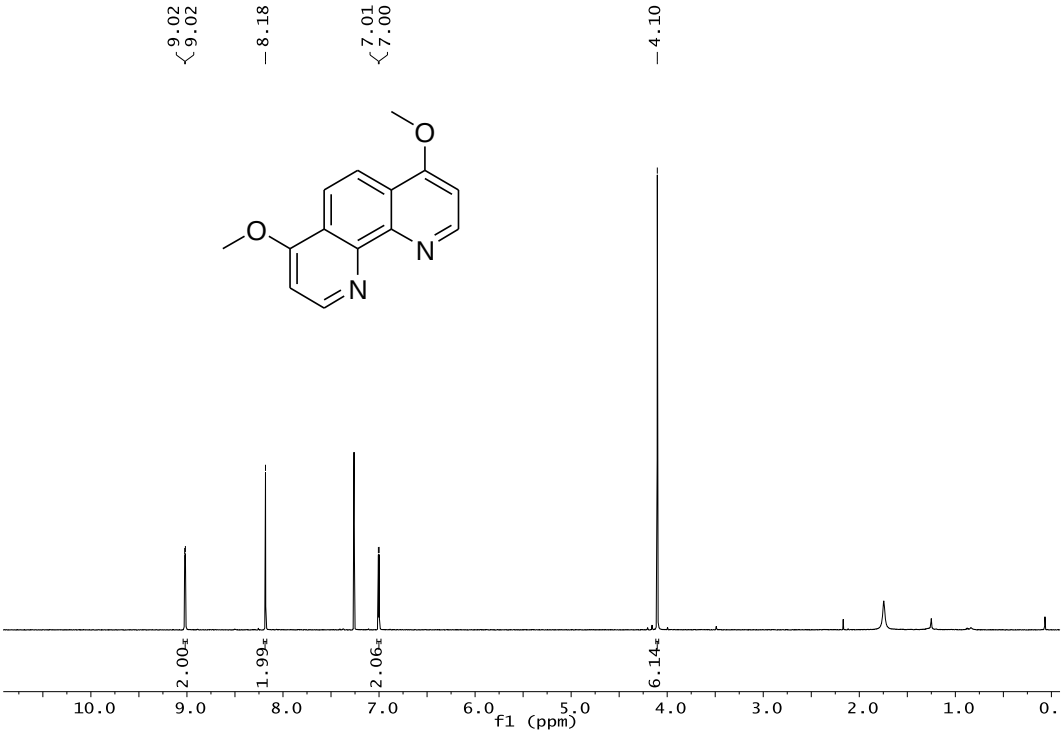
^{13}C NMR (176 MHz, $CDCl_3$) - 341



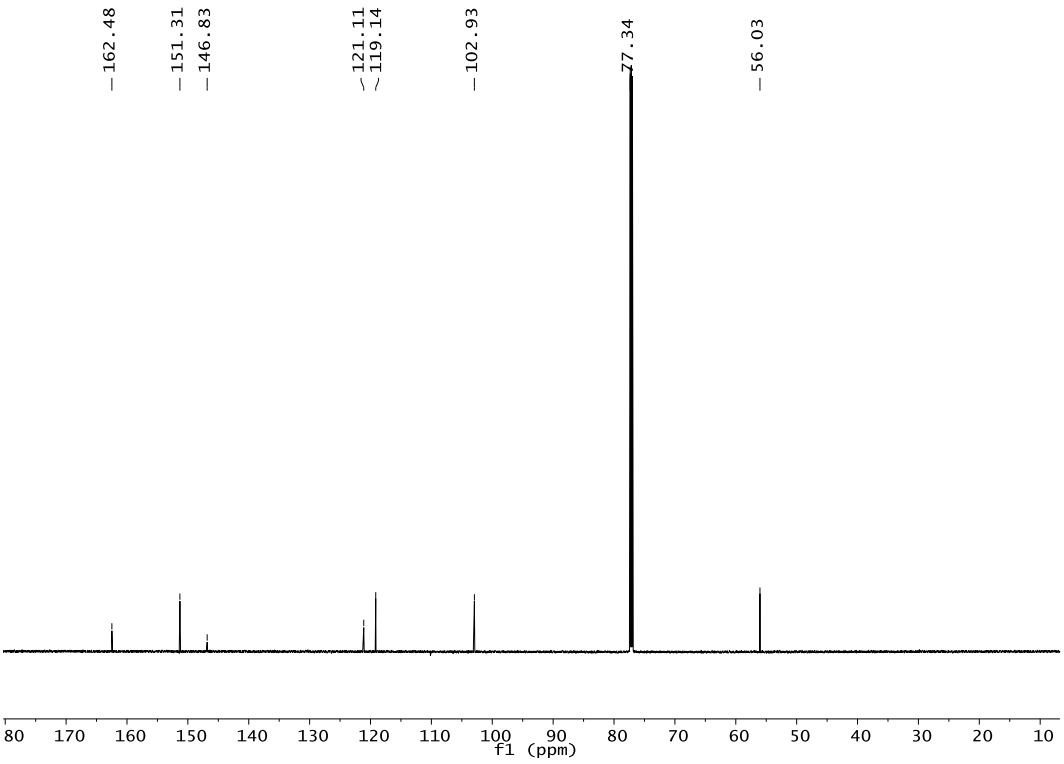
^{1}H NMR (400 MHz, NaOD) - 342



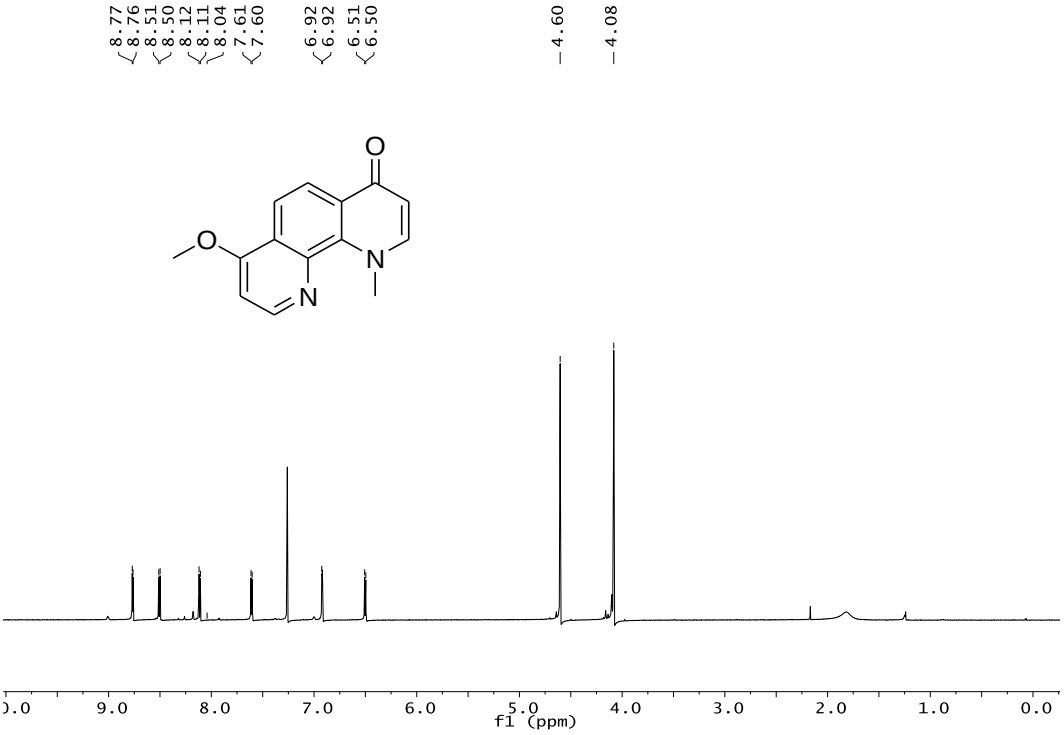
^{1}H NMR (700 MHz, $CDCl_3$) - 343



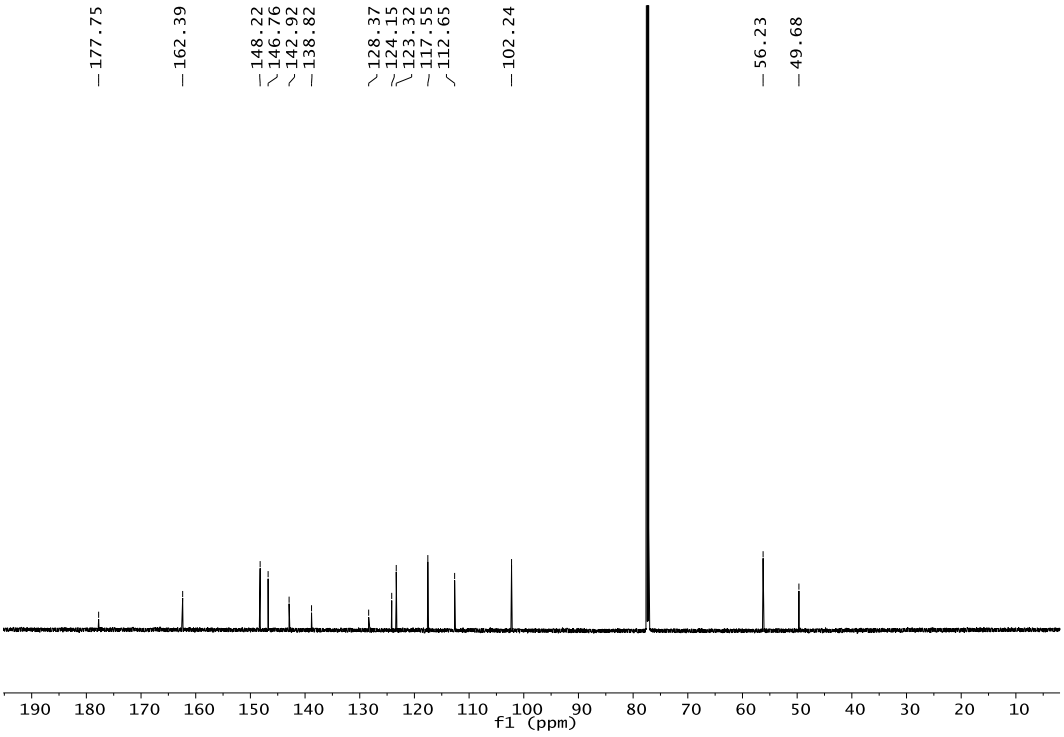
^{1}H NMR (176 MHz, $CDCl_3$) - 343



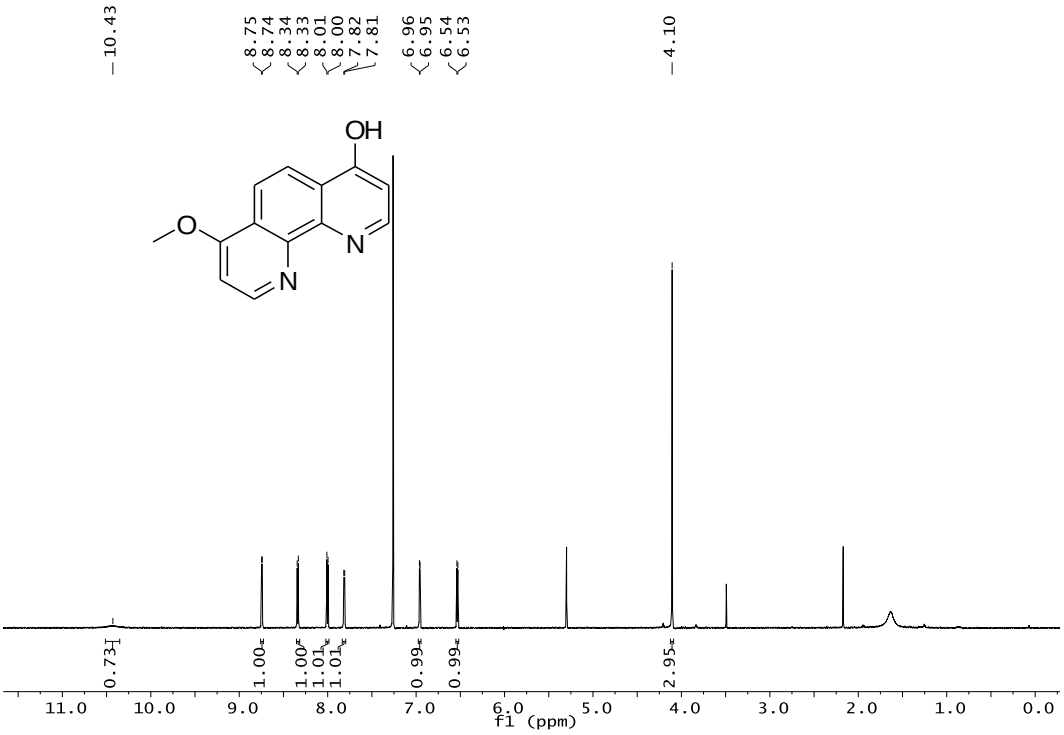
^{1}H NMR (700 MHz, $CDCl_3$) - 344



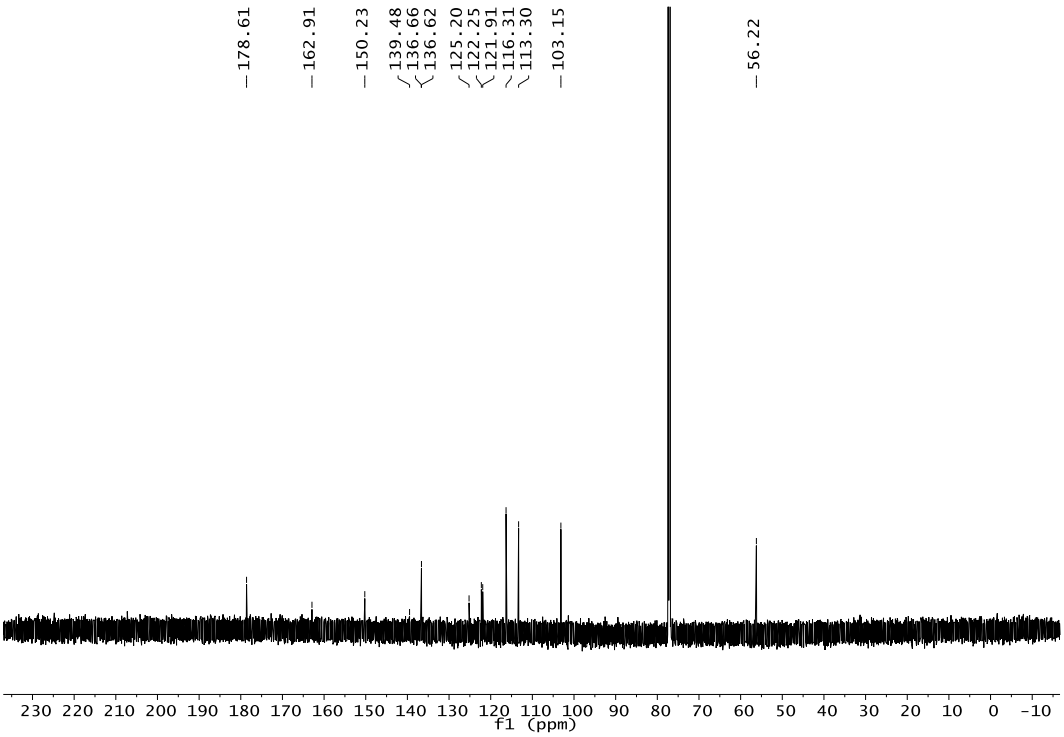
^{13}C NMR (176 MHz, $CDCl_3$) - 344



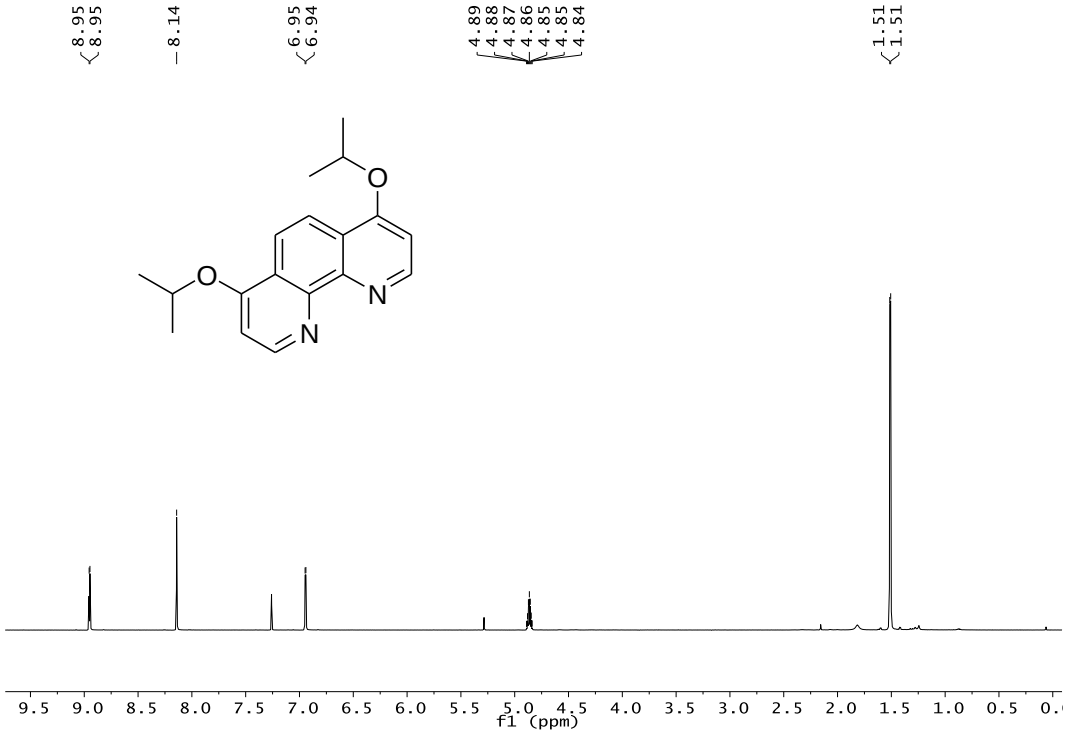
^{1}H NMR (700 MHz, $CDCl_3$) - 345



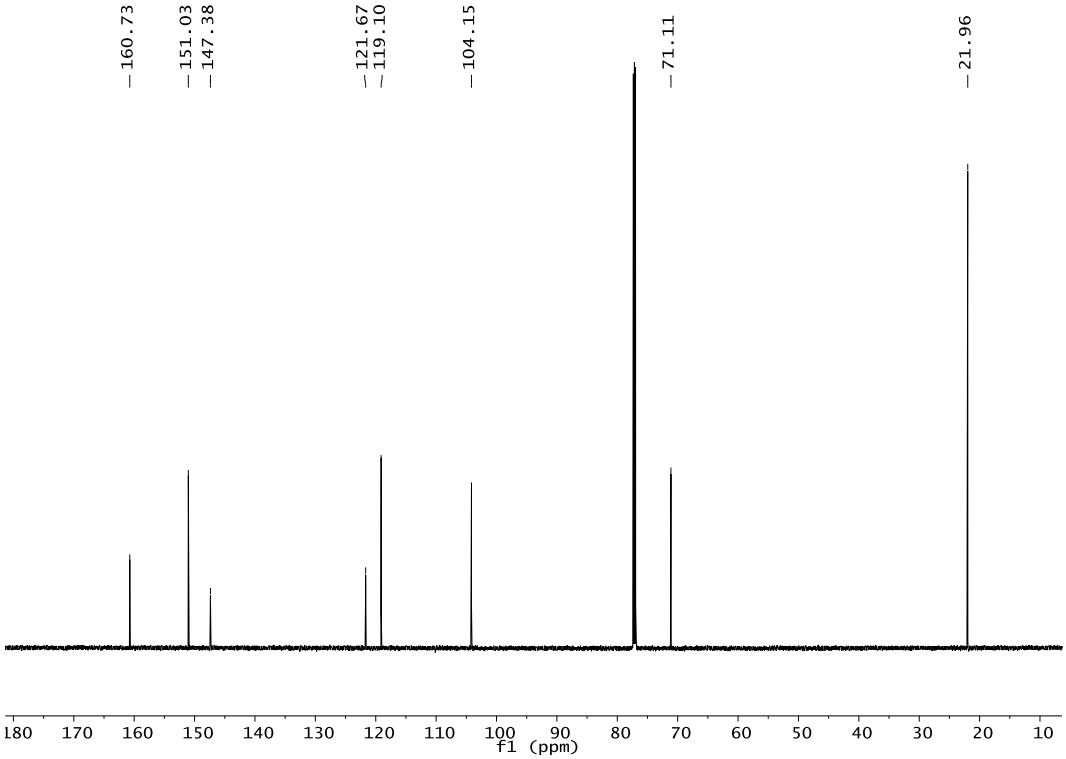
^{13}C NMR (176 MHz, $CDCl_3$) - 345



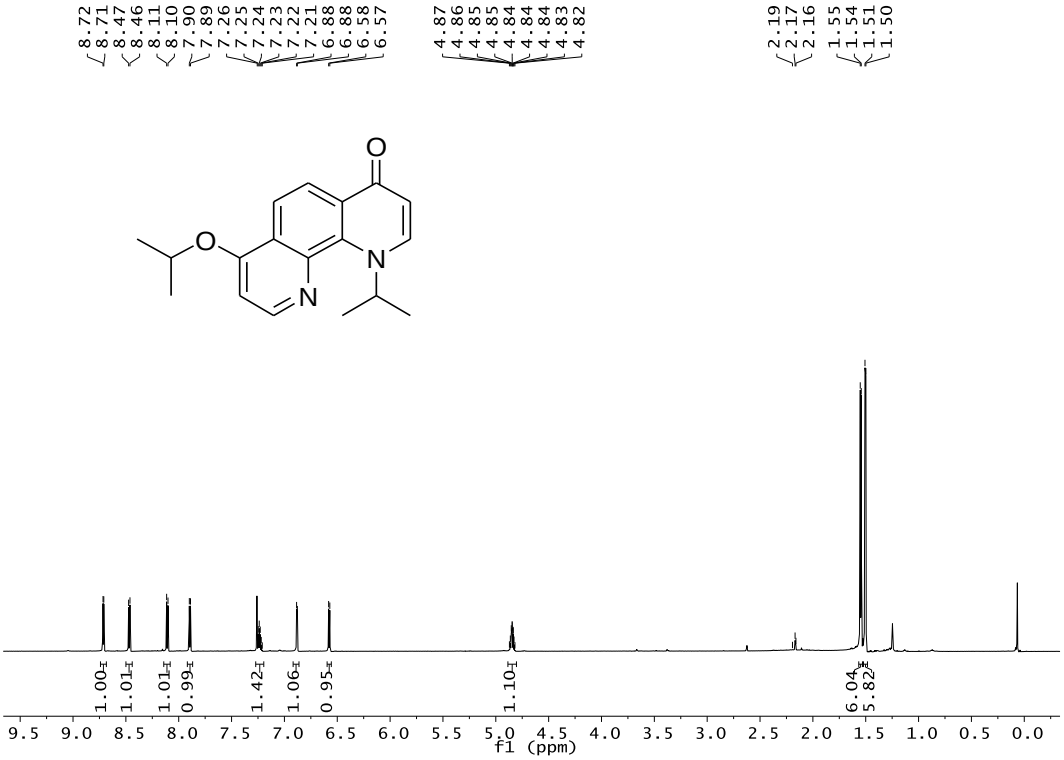
^{1}H NMR (700 MHz, $CDCl_3$) - 347



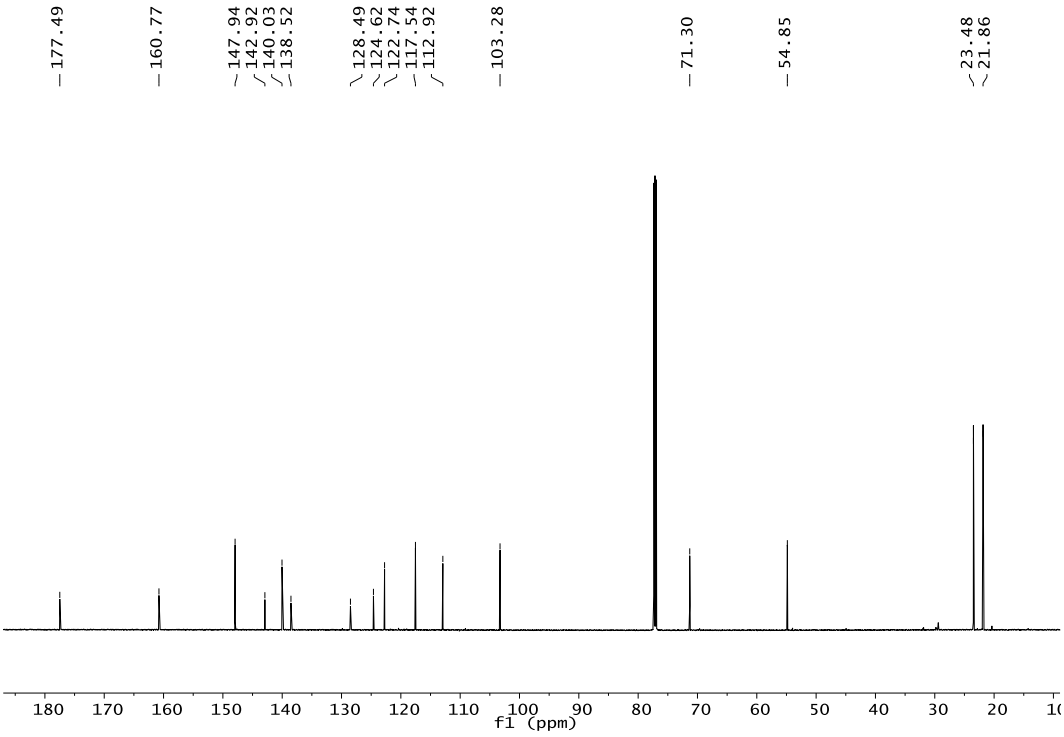
^{13}C NMR (176 MHz, $CDCl_3$) - 347



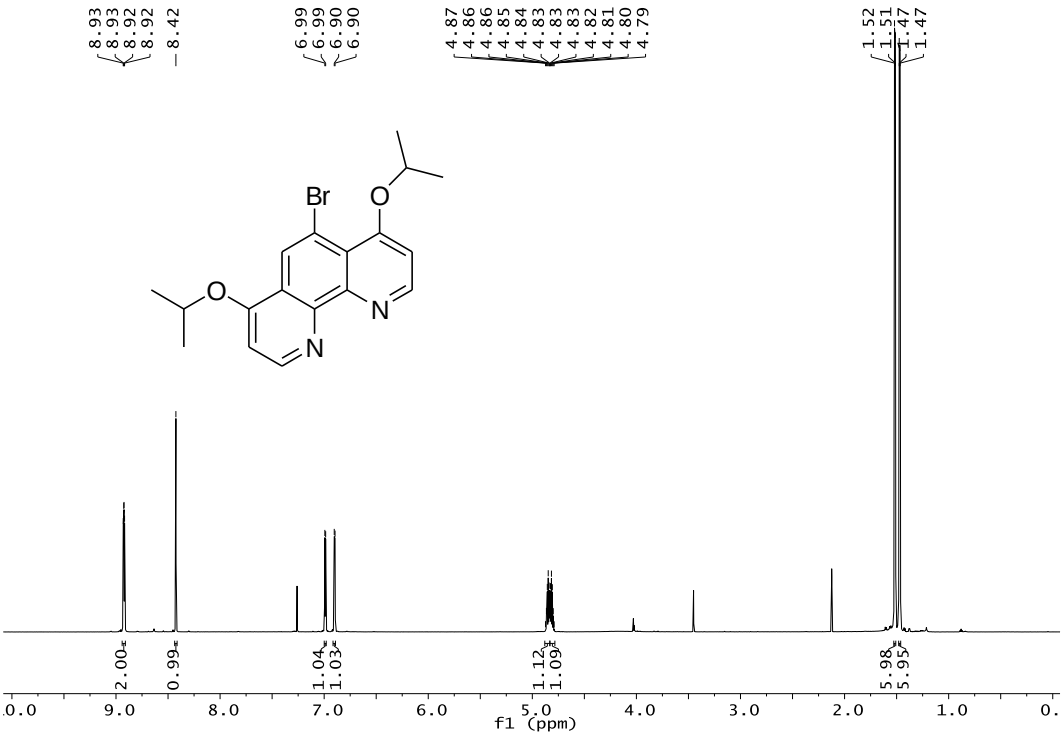
^{1}H NMR (700 MHz, $CDCl_3$) - 349



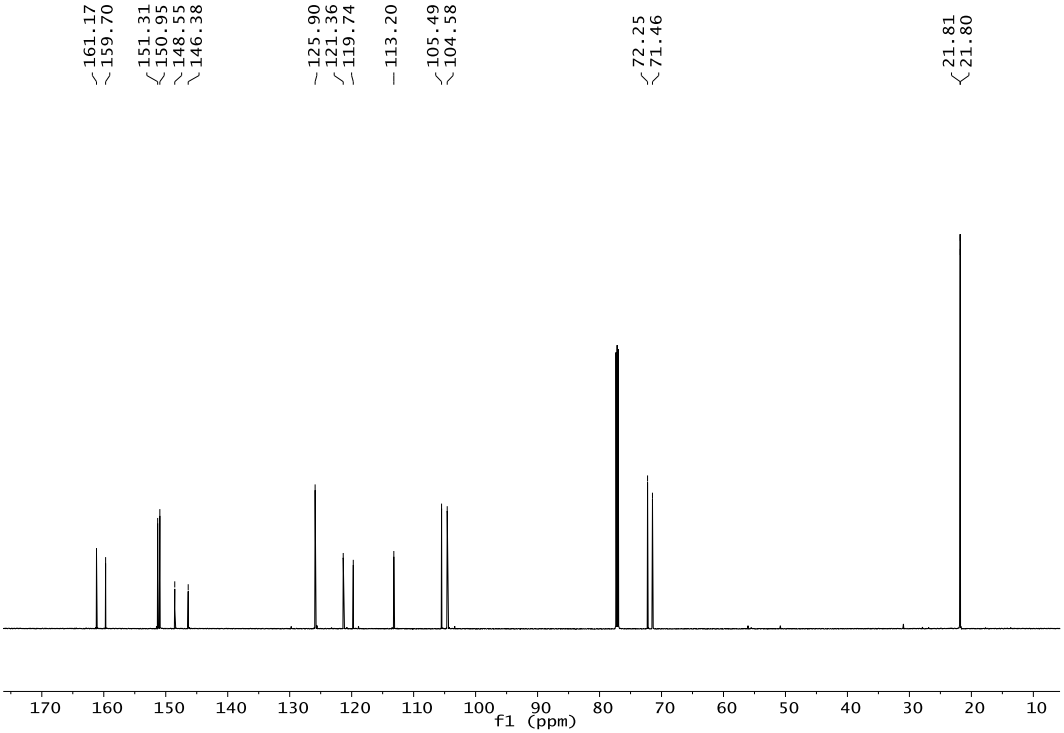
^{13}C NMR (176 MHz, $CDCl_3$) - 349



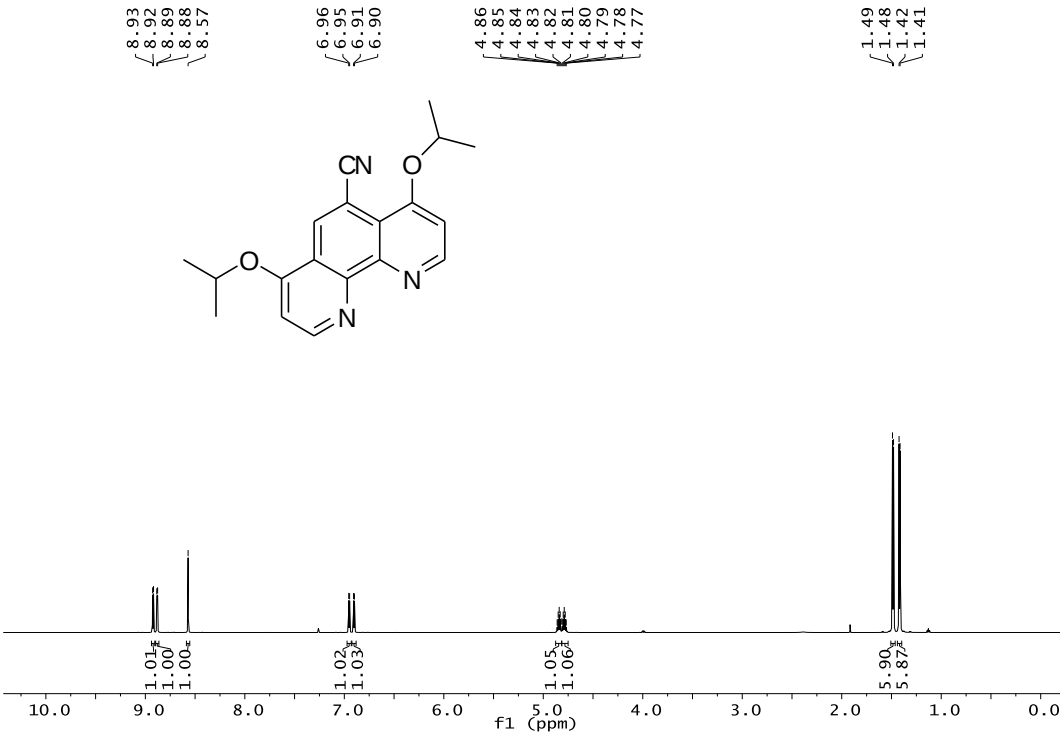
^{1}H NMR (700 MHz, $CDCl_3$) - 350



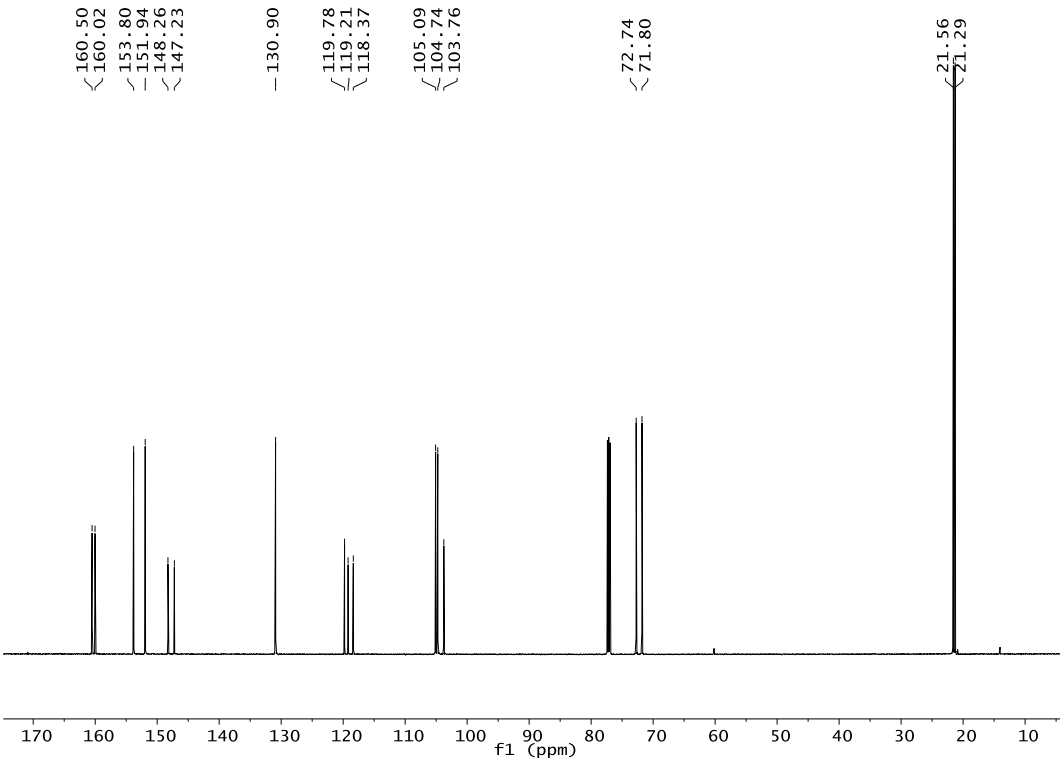
^{13}C NMR (176 MHz, $CDCl_3$) - 350



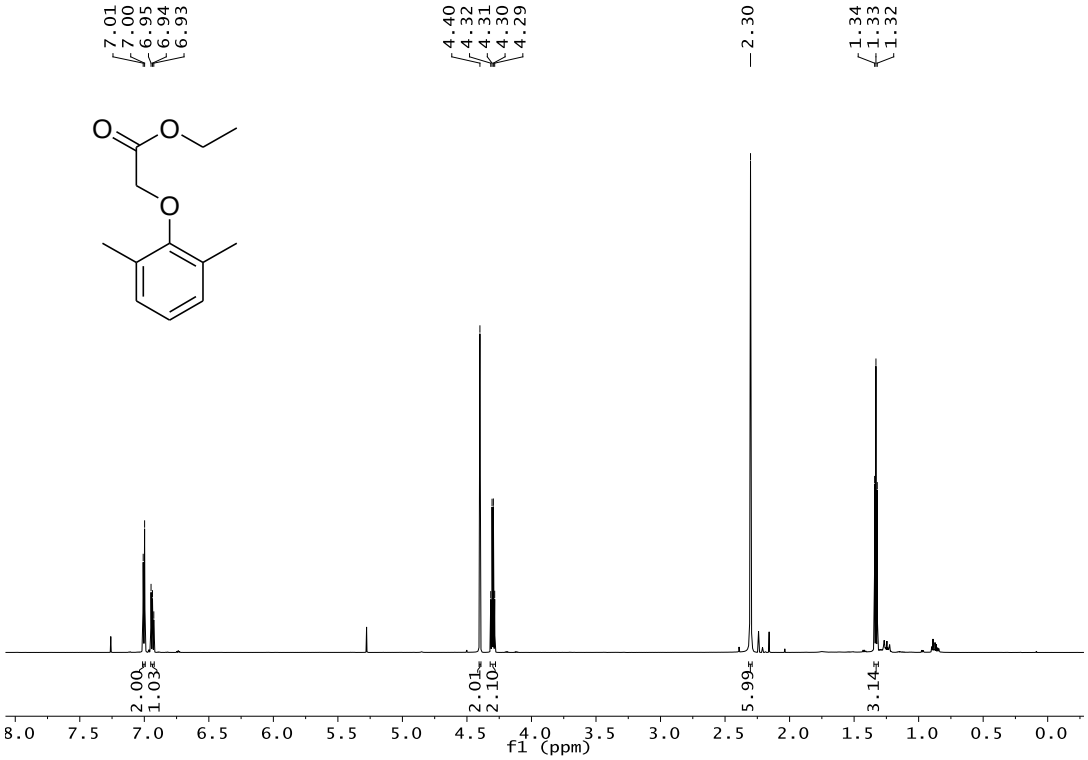
^{1}H NMR (600 MHz, $CDCl_3$) - 351



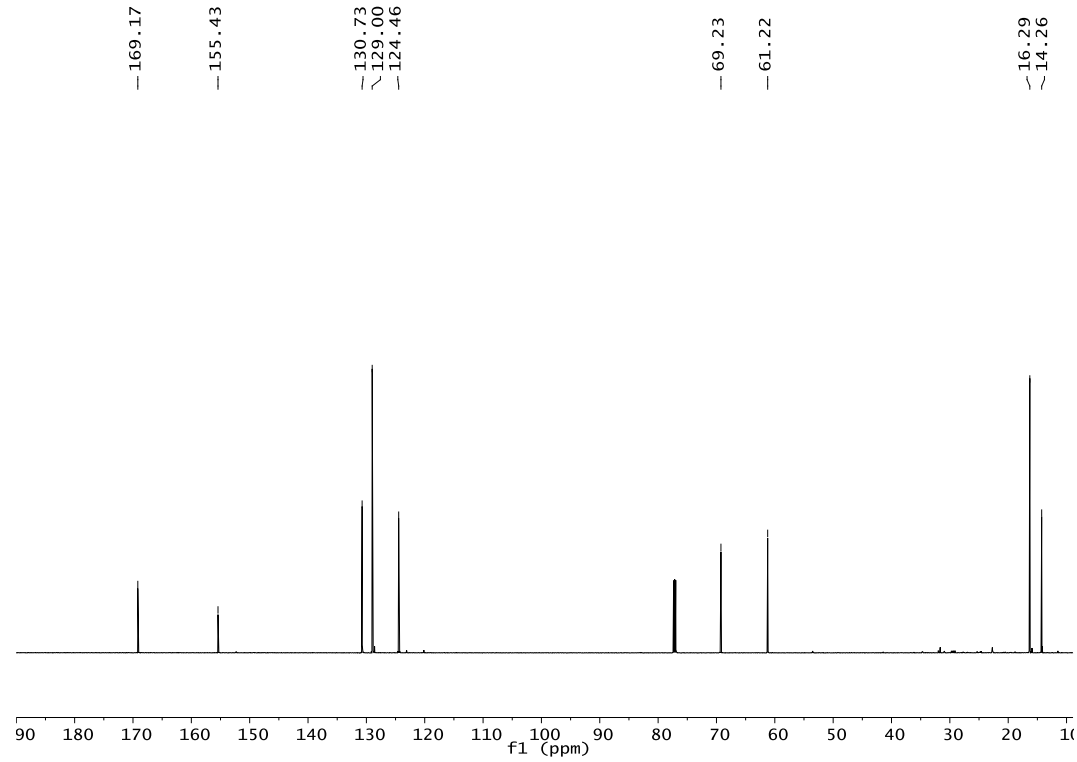
^{13}C NMR (151 MHz, $CDCl_3$) - 351



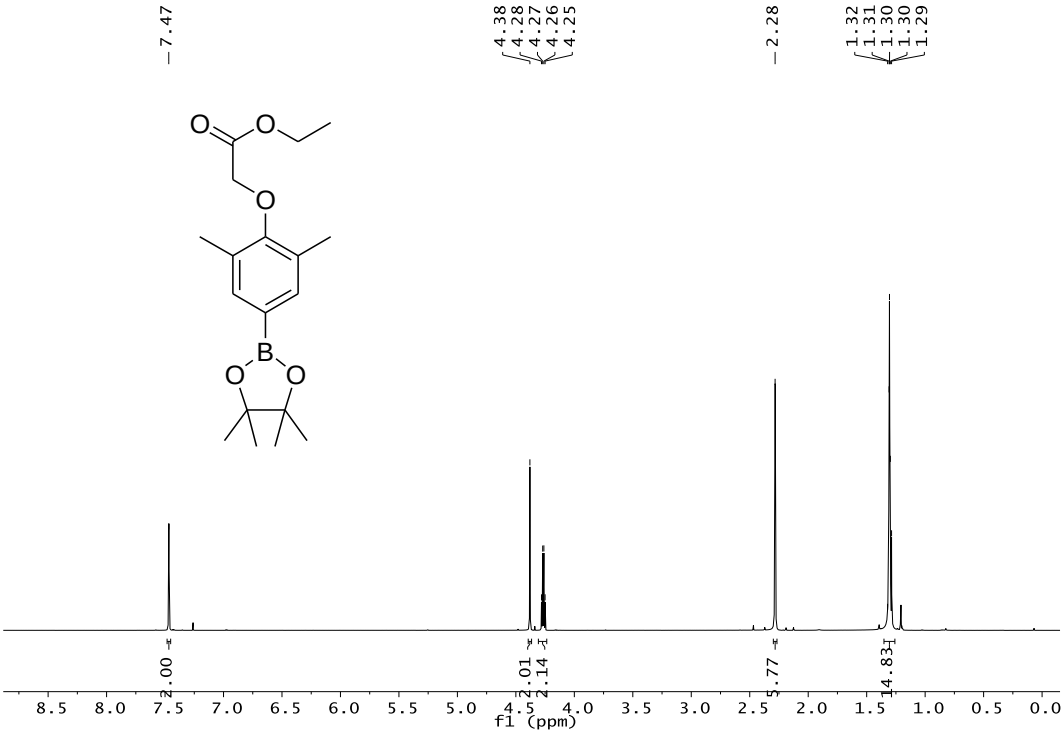
^{1}H NMR (700 MHz, $CDCl_3$) - 353



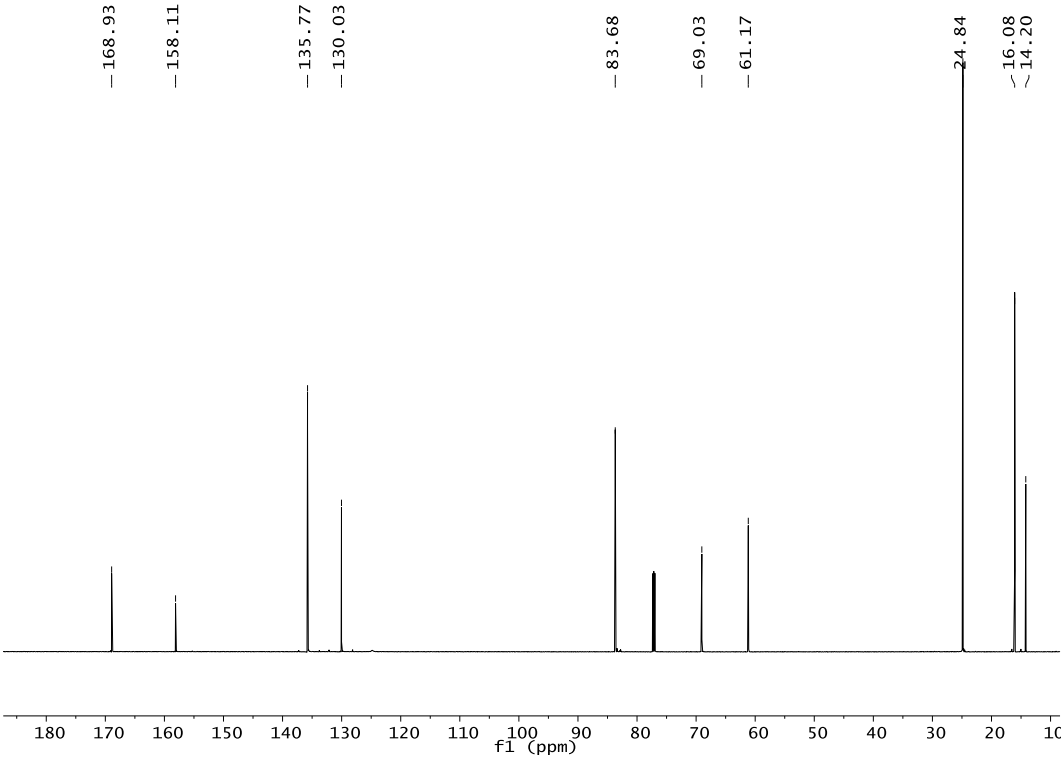
^{13}C NMR (176 MHz, $CDCl_3$) - 353



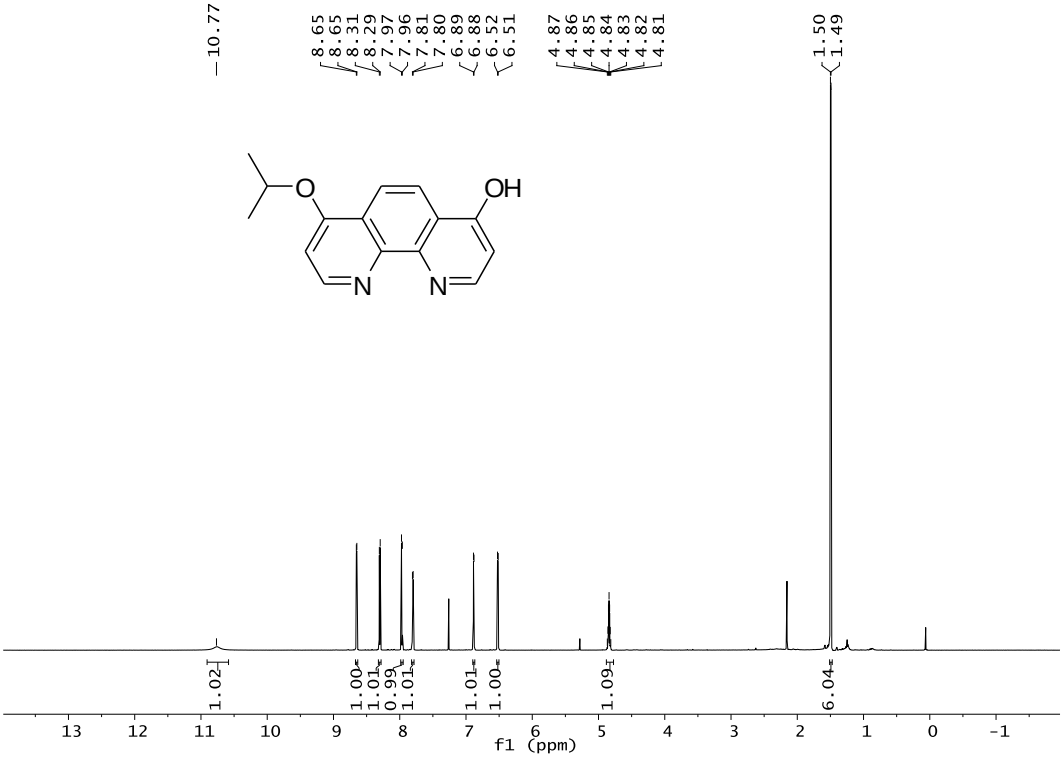
^{1}H NMR (700 MHz, $CDCl_3$) - 354



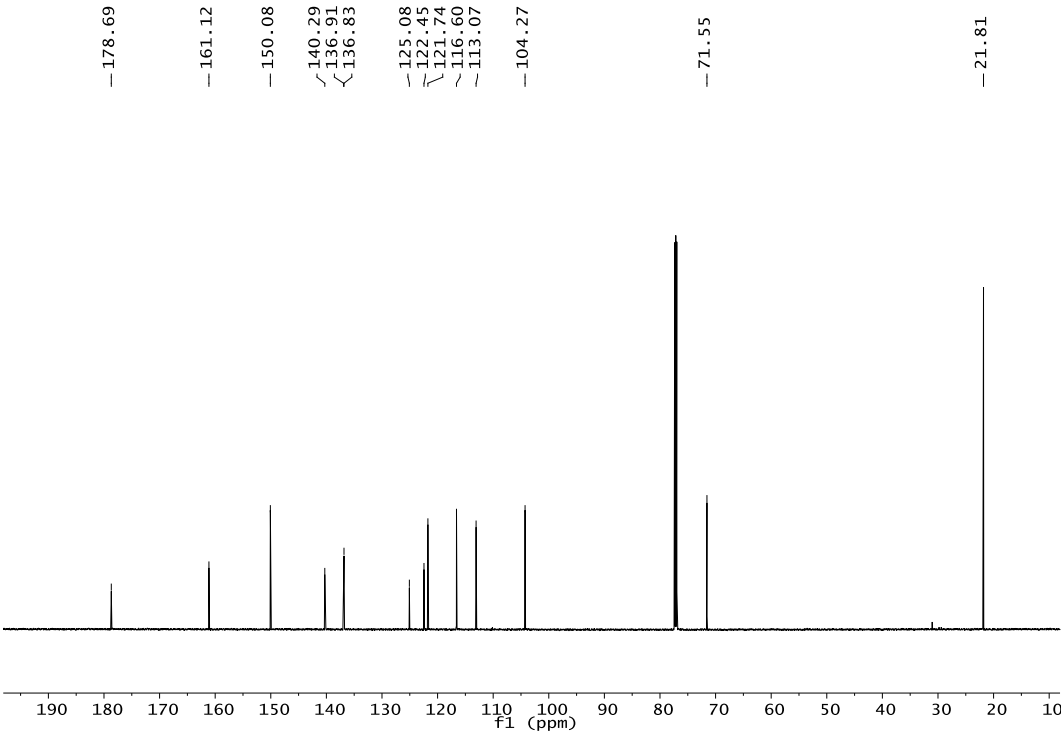
^{13}C NMR (176 MHz, $CDCl_3$) - 354



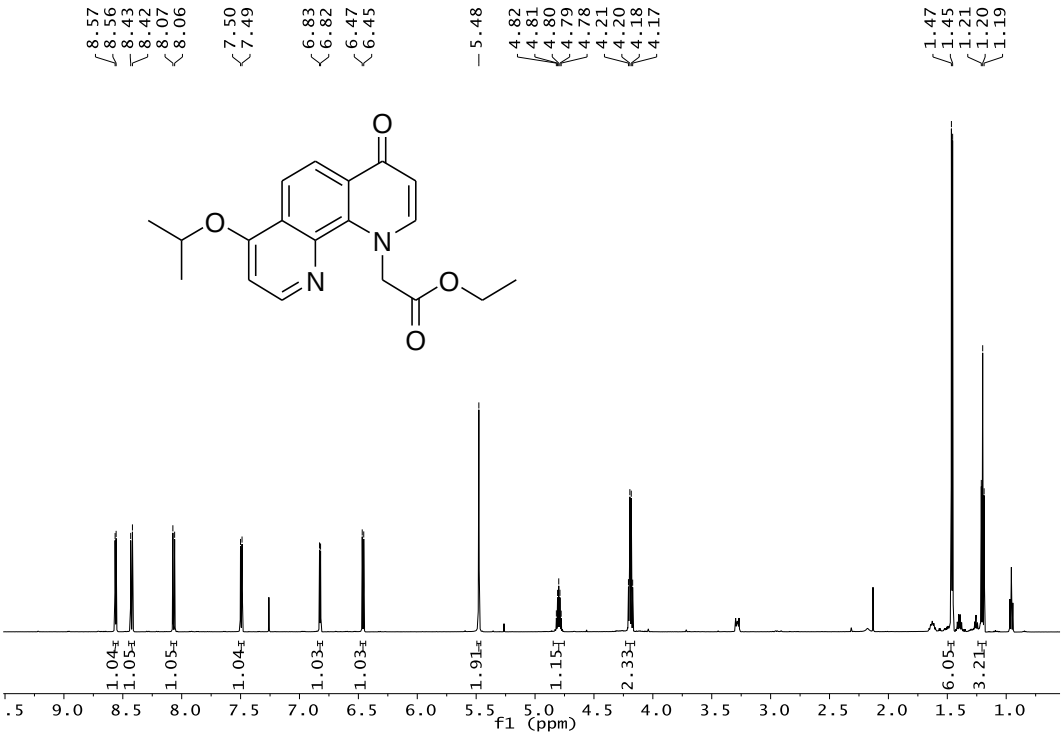
^{1}H NMR (700 MHz, $CDCl_3$) - 348



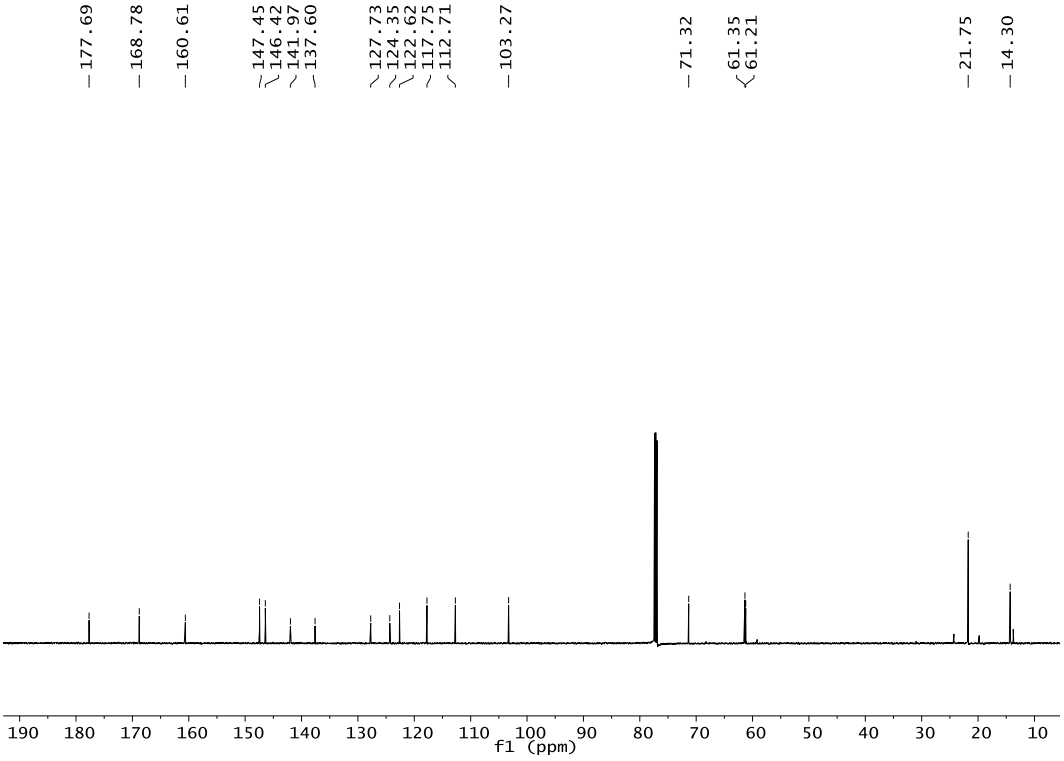
^{13}C NMR (176 MHz, $CDCl_3$) - 348



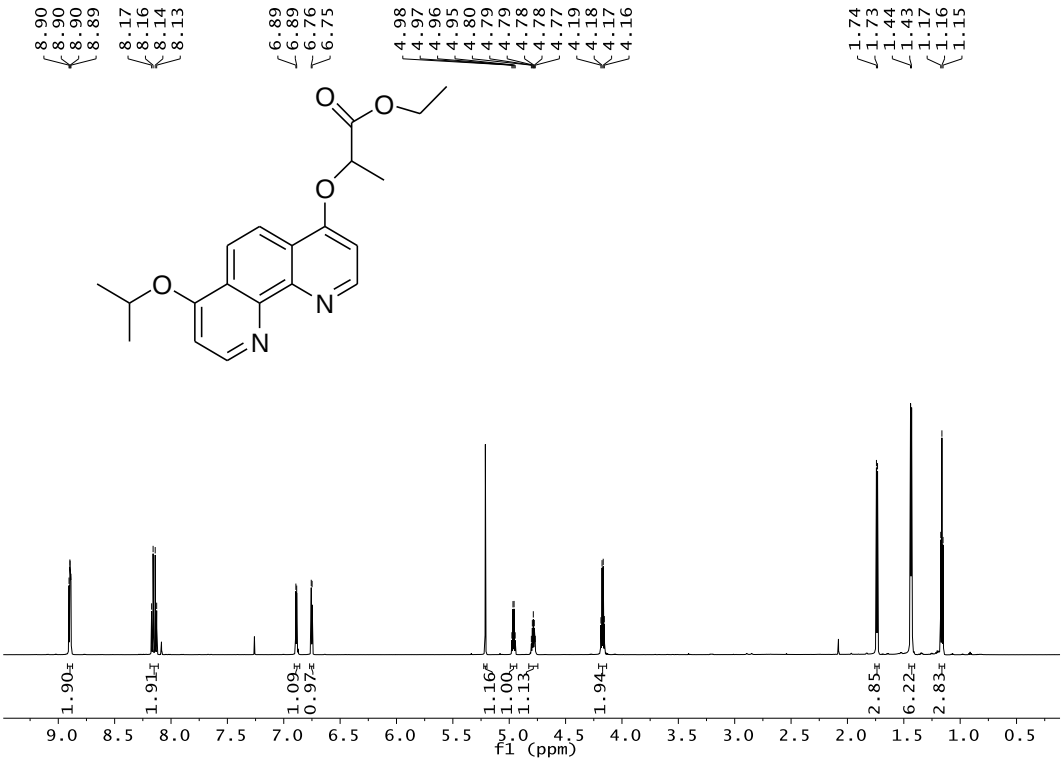
^{1}H NMR (600 MHz, $CDCl_3$) - 370



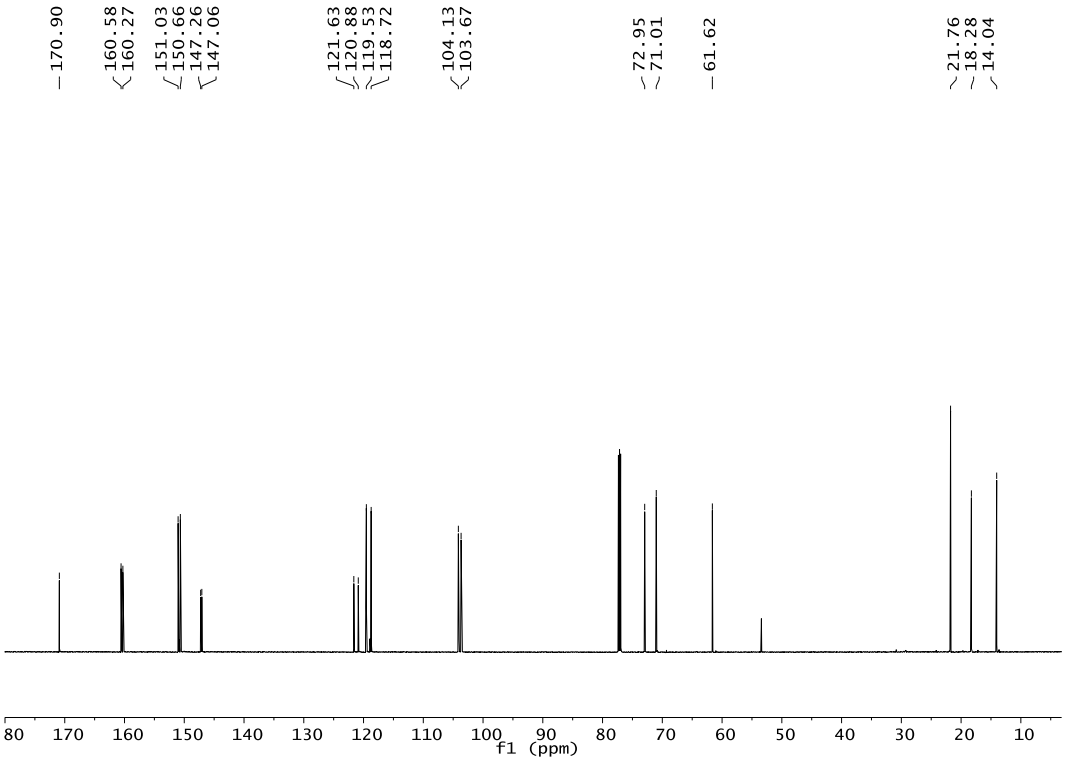
^{13}C NMR (151 MHz, $CDCl_3$) - 370



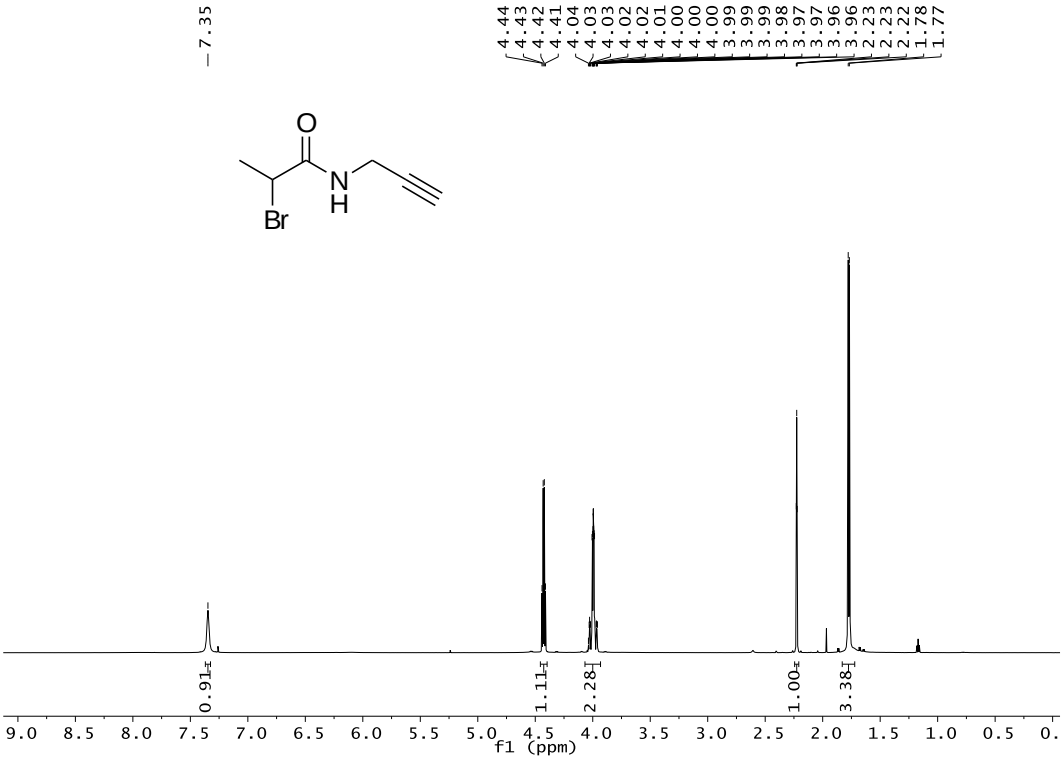
^{1}H NMR (700 MHz, $CDCl_3$) - 367



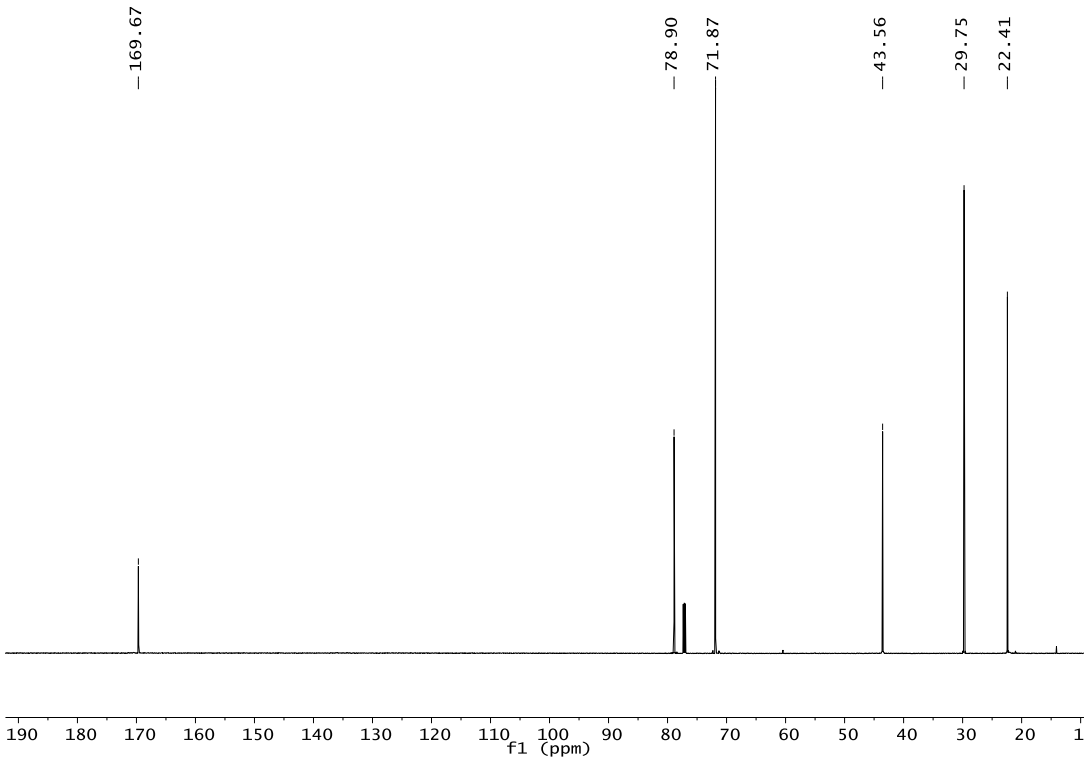
^{13}C NMR (176 MHz, $CDCl_3$) - 367



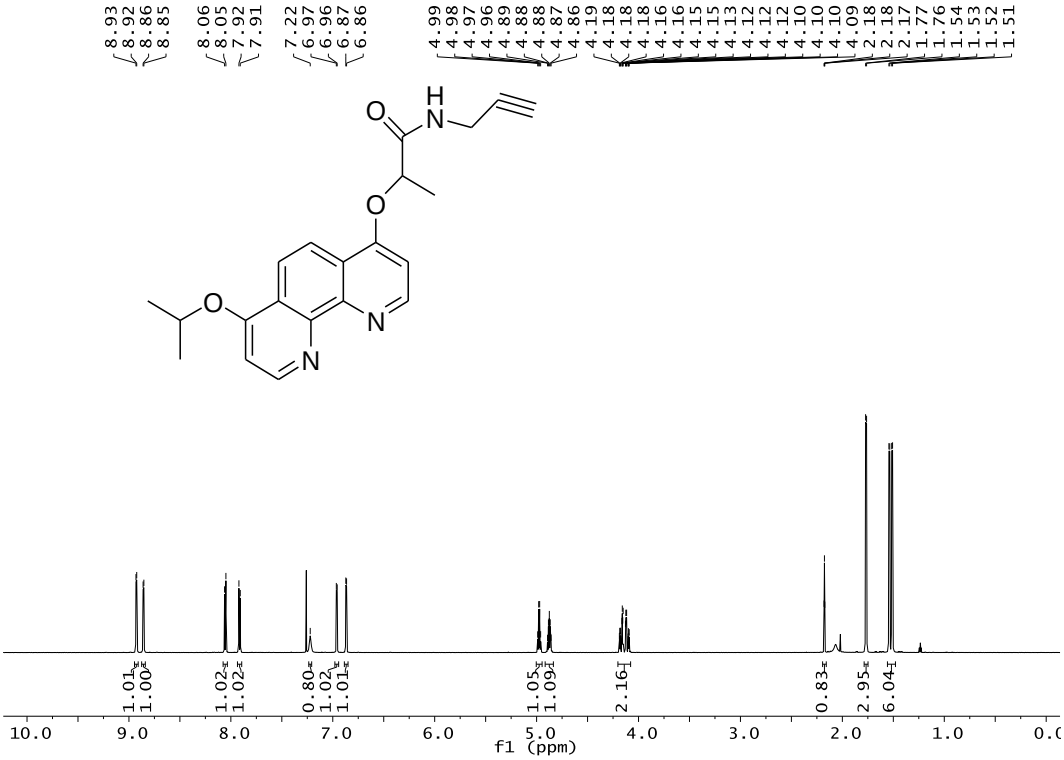
^{1}H NMR (700 MHz, $CDCl_3$) - 378



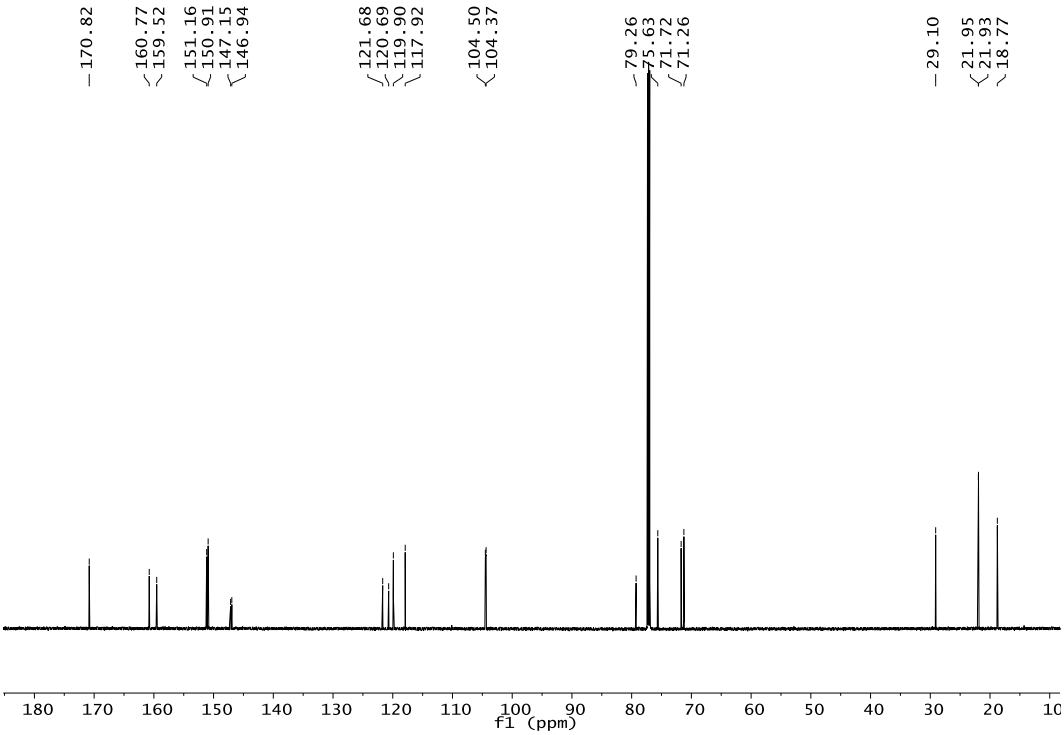
^{13}C NMR (176 MHz, $CDCl_3$) - 378



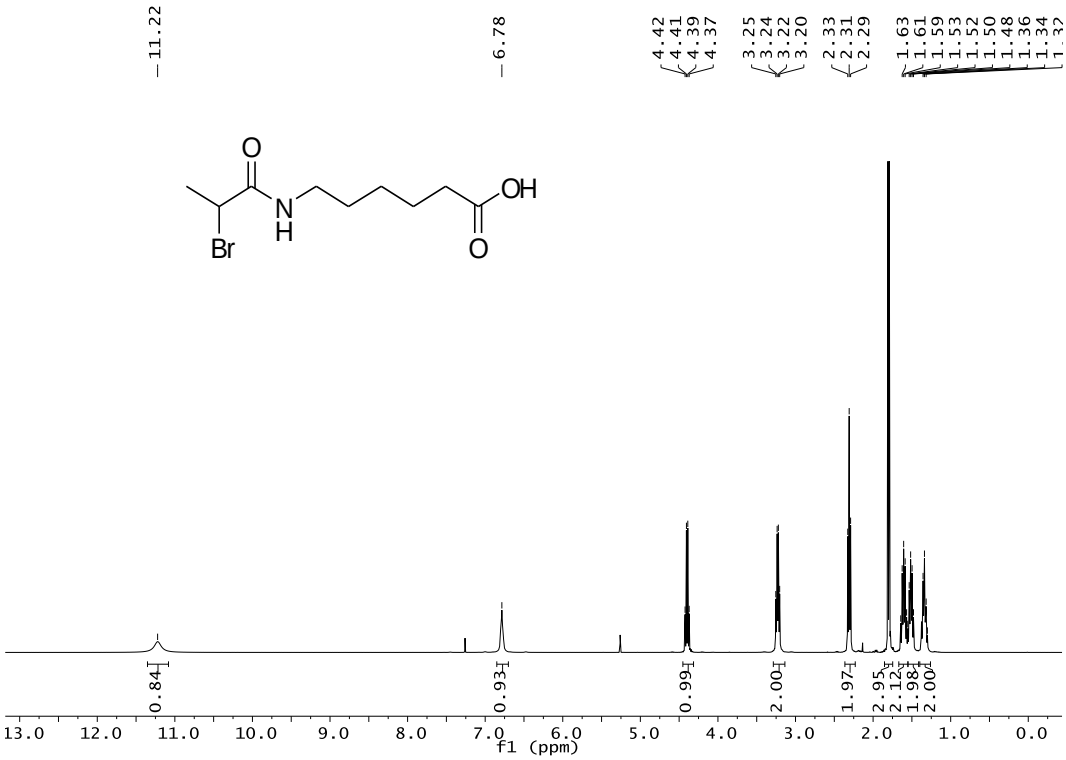
^{1}H NMR (700 MHz, $CDCl_3$) - 379



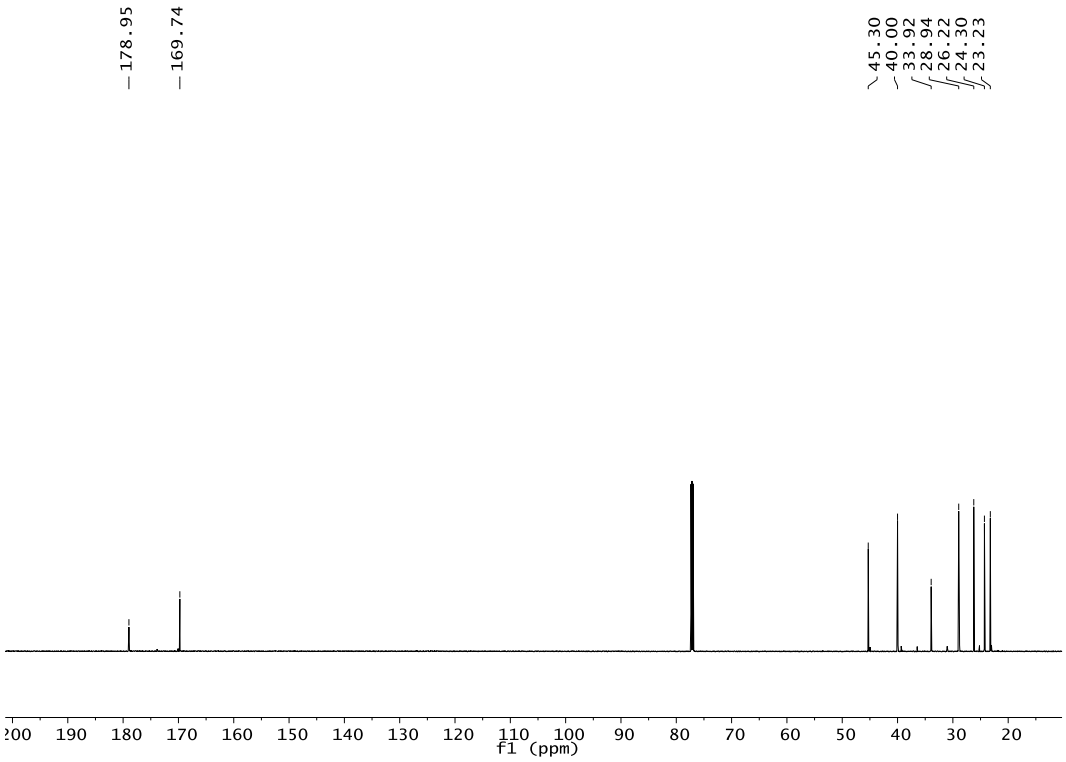
^{13}C NMR (176 MHz, $CDCl_3$) - 379



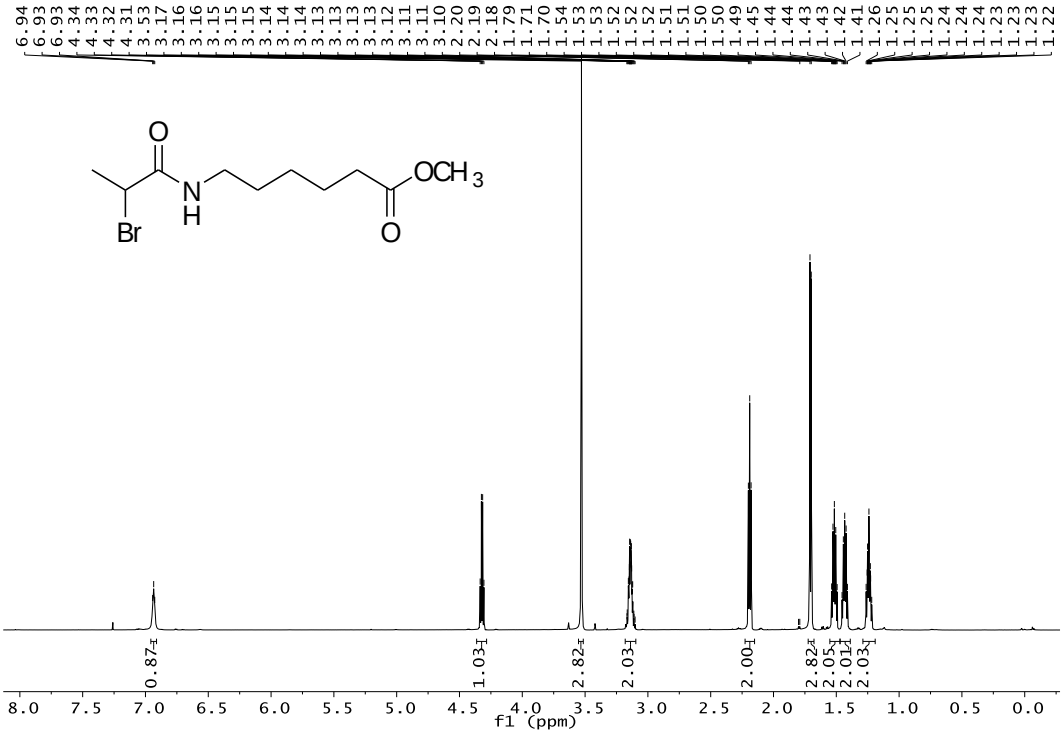
^{1}H NMR (700 MHz, $CDCl_3$) - 381



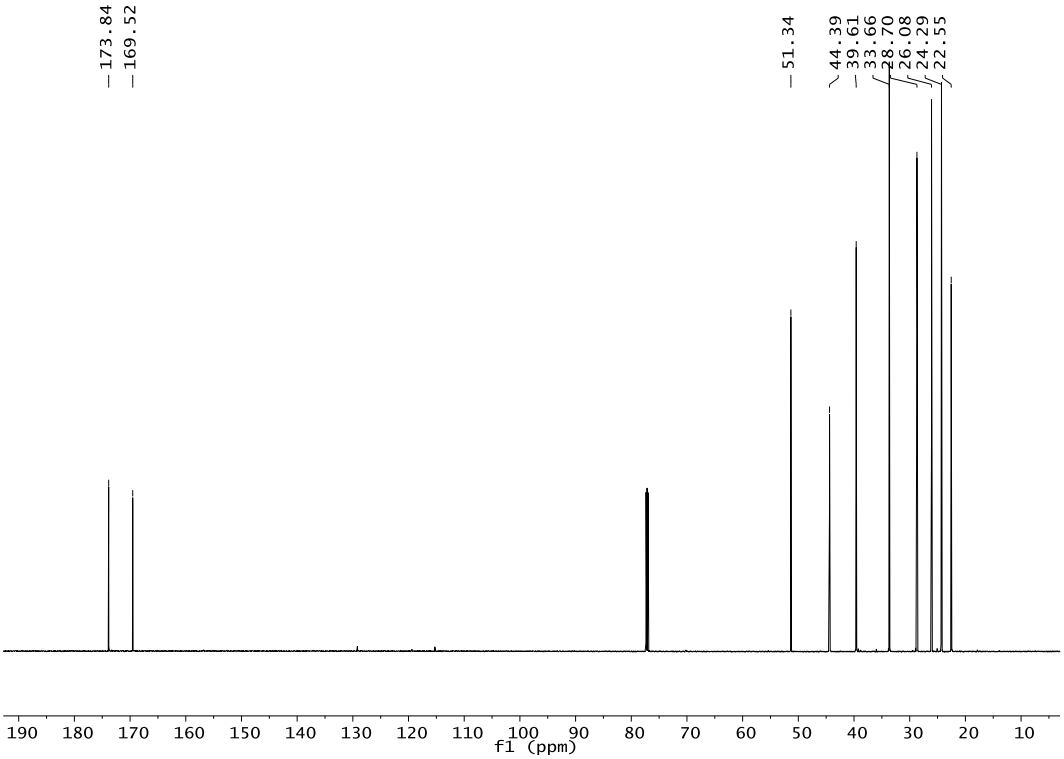
^{13}C NMR (176 MHz, $CDCl_3$) - 381



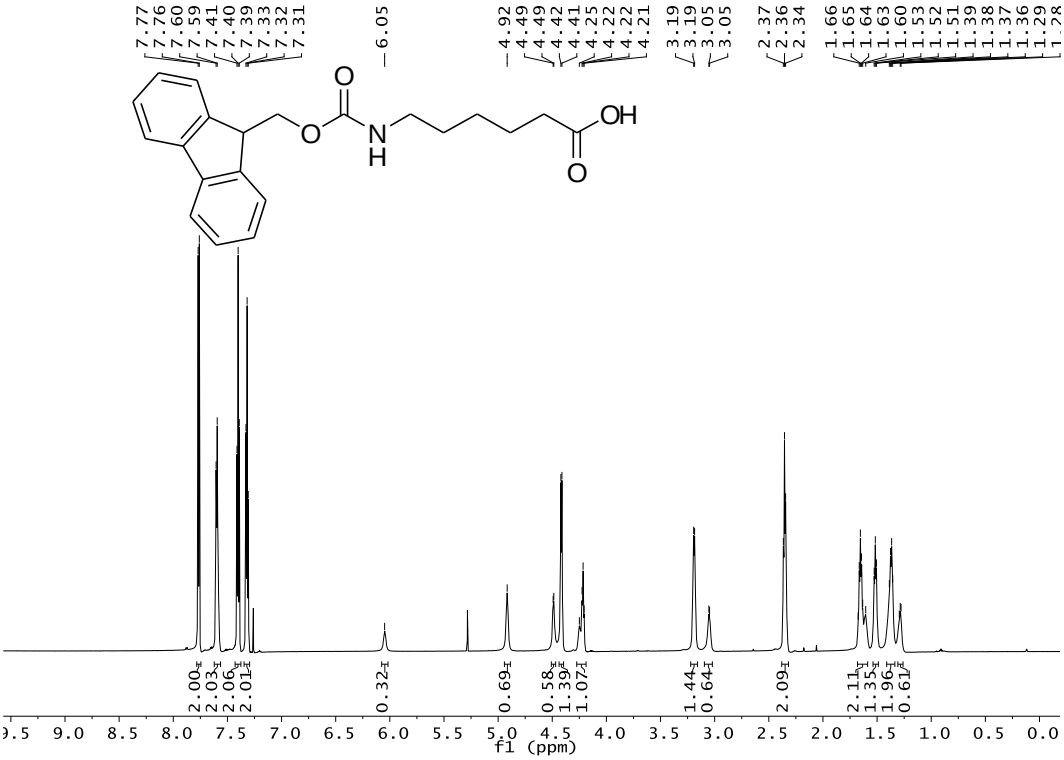
^{1}H NMR (700 MHz, $CDCl_3$) - 383



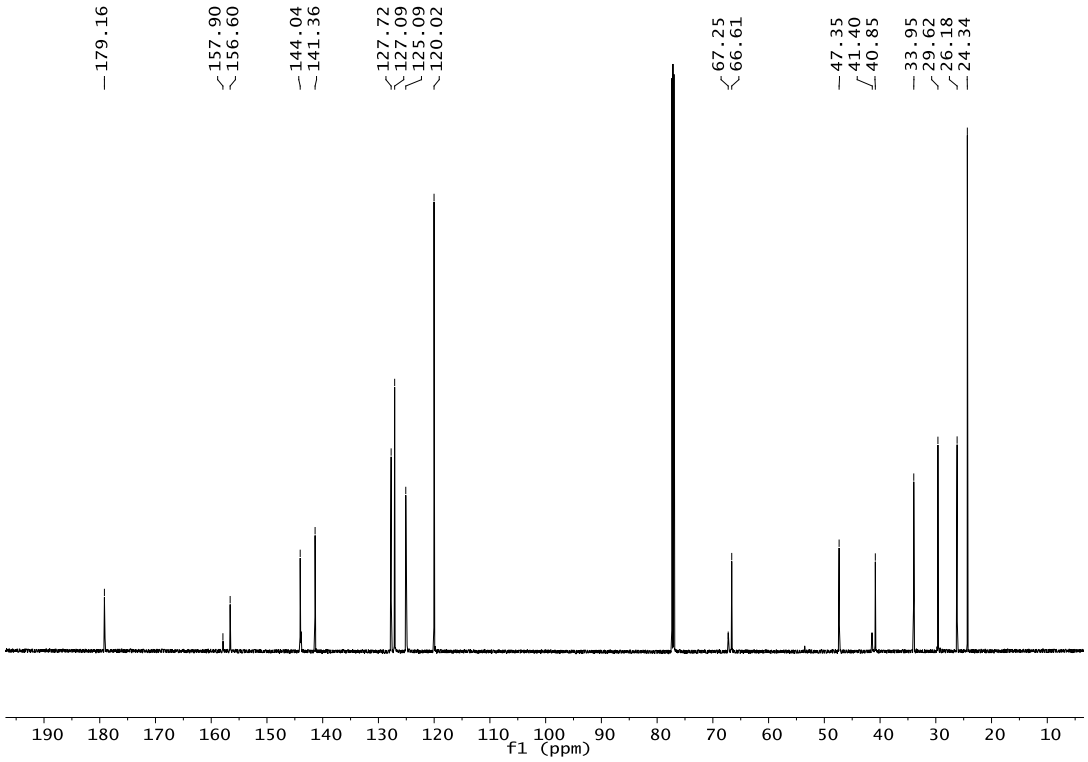
^{13}C NMR (176 MHz, $CDCl_3$) - 383



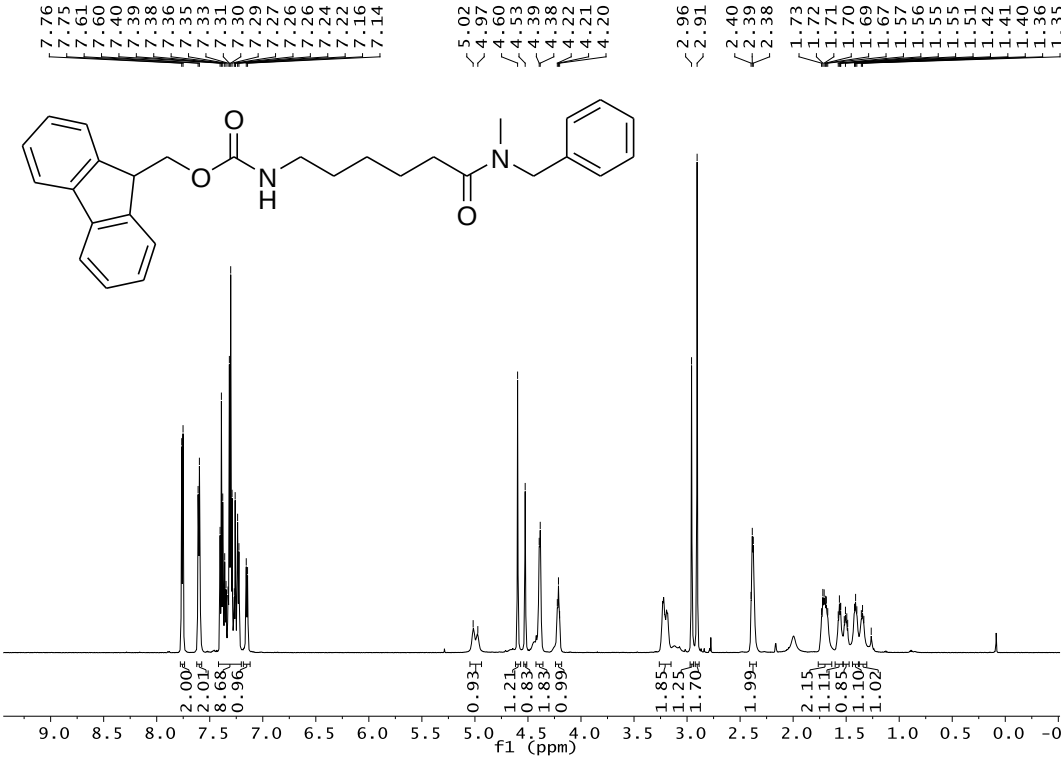
^{1}H NMR (700 MHz, $CDCl_3$) – 389



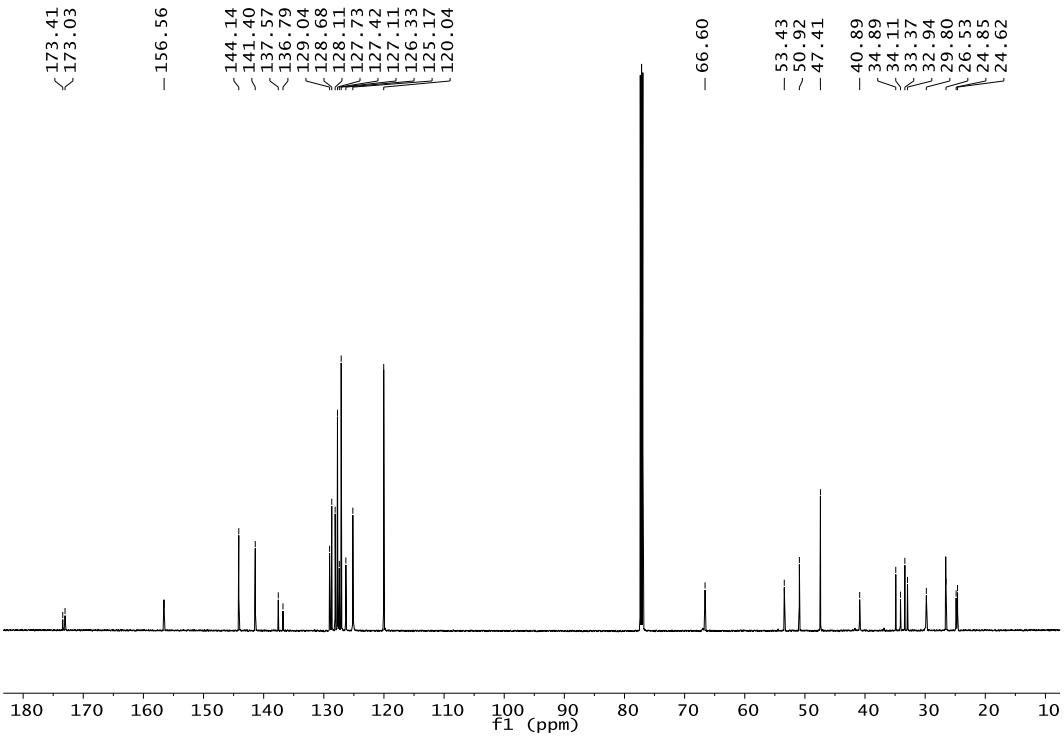
^{13}C NMR (176 MHz, $CDCl_3$) - 389



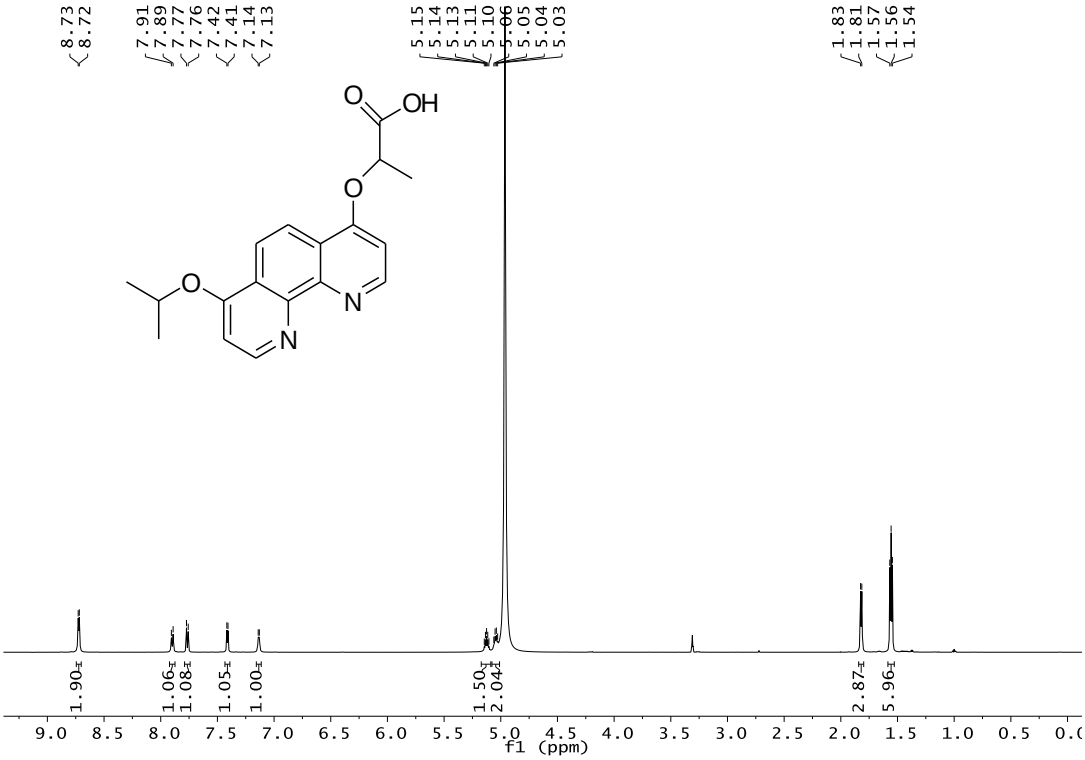
^{1}H NMR (600 MHz, $CDCl_3$) - 393



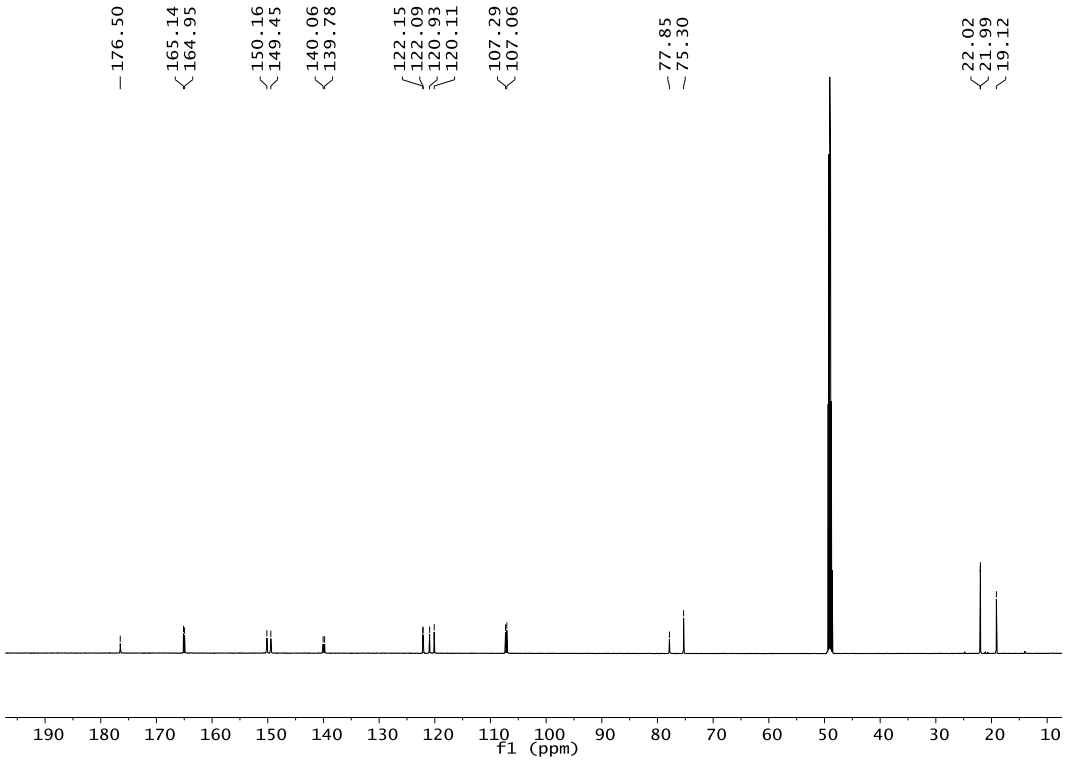
^{13}C NMR (151 MHz, $CDCl_3$) - 393



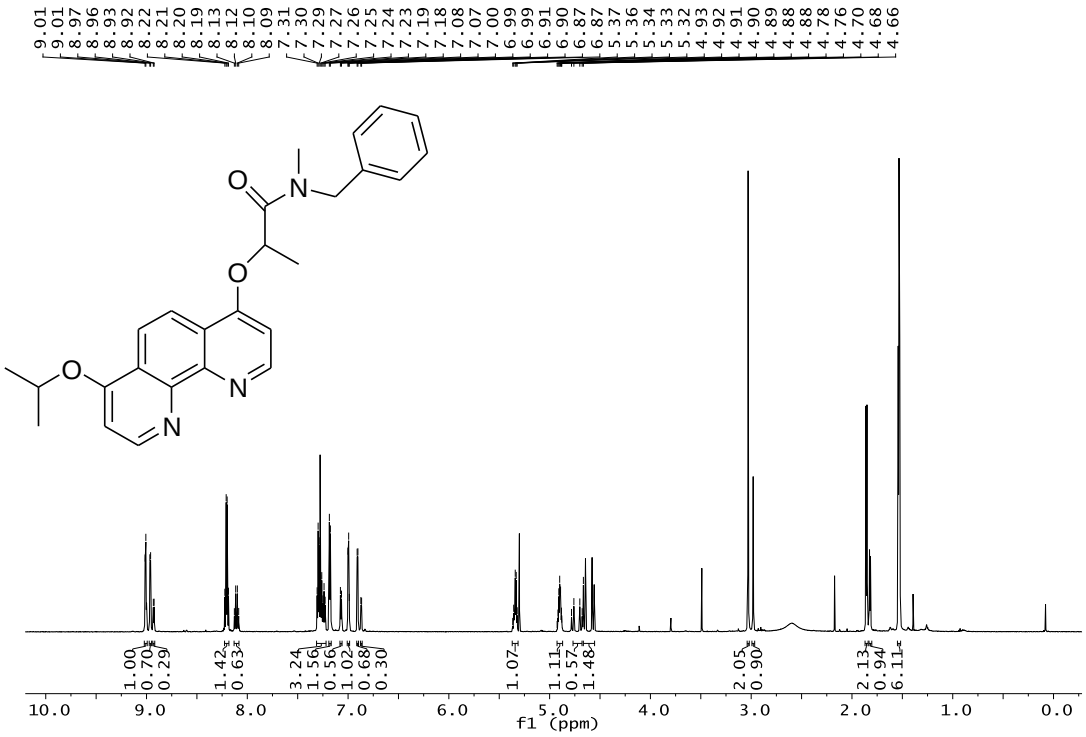
^{1}H NMR (600 MHz, $CDCl_3$) - 395



^{13}C NMR (151 MHz, $CDCl_3$) - 395



^{1}H NMR (700 MHz, $CDCl_3$) - 396



^{13}C NMR (176 MHz, $CDCl_3$) - 396